REMARKS

Claims 29-40 are pending in the application. Claims 1-28 are cancelled, claims 29-36 were previously pending, and new claims 37-40 are added by this amendment. These new claims have support throughout the specification, and specifically at page 4, lines 15-20. No new matter has been added by the addition of these claims.

Formal Matters

The Examiner indicated that the application is not in compliance with the sequence rules because the sequences in Figure 1 are not accompanied by reference to SEQ ID NOS:. The Description of the Drawings section of the application has been amended to include a reference to SEQ ID NOS:1 and 2 in the drawings. In light of this amendment, Applicants request that the Examiner withdraw this objection.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 29-36 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner contends that claims 29-36 do not enable one skilled in the art to make and/or use the invention.

The Examiner bases the rejection on two premises: (1) that BMP-12, BMP-13, and MP-52 preferentially enhance the growth of tendon and/or ligament tissue; and (2) that neither tendonitis nor carpal tunnel syndrome is characterized by loss of tendon or ligament tissue. The Examiner then argues that tendonitis and carpal tunnel syndrome cannot be treated by enhancing the growth of tendon and/or ligament tissue because the enhancement of tendon/ligament tissue will not reduce the inflammation and pain associated with these conditions. Applicants disagree.

The Examiner's argument that tendonitis and carpal tunnel syndrome may only be treated by agents that directly reduce inflammation and pain is incorrect. Damage to tendon tissue is the overwhelming cause of the inflammatory response and pain that make up the symptoms of tendonitis and carpal tunnel syndrome. The inflammation and pain associated with these conditions does not occur in the absence of tissue damage. In particular, the attached table of definitions describes tendonitis as a tendon strain or tear (Leadbetter, *Clinics in Sports Medicine* 11(2):533, 545 (1992)). Carpal tunnel syndrome is caused by damaged and enlarged tendons and ligaments, which pinch a nerve in the wrist (see Carpal Tunnel Syndrome Information Page from NINDS).

Treating the tendon/ligament damage causing the inflammation and pain will result in an overall reduction in the symptoms of tendonitis and carpal tunnel syndrome. As the Examiner acknowledges, BMP-12, BMP-13, and MP-52 can all enhance tendon and ligament formation. Thus, they can also induce the growth of damaged tendon and ligament tissue. This new tendon/ligament growth will reduce tissue damage and will eventually lead to a reduction in the manifested symptoms of tendonitis and carpal tunnel syndrome, inflammation and pain. Applicants submit that no undue experimentation would be needed to demonstrate that BMP-12, BMP-13, and MP-52 can treat tendonitis and carpal tunnel syndrome, and thus the claims are enabled.

Nevertheless, and in an effort to further prosecution, Applicants have added new claims 37-40, which recite a method for treating a tendon or ligament defect. Applicants respectfully request that the Examiner withdraw the rejection of claims 29-36 under 35 U.S.C. § 112, first paragraph.

Double Patenting Rejection

The Examiner rejected claims 29-36 under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of U.S. Patent No. 5,658,882.

Applicants file herewith a terminal disclaimer under 37 C.F.R. §1.321(c) indicating that the '882 patent and the instant application are commonly owned. Applicants note that any patent issuing from this patent would expire on December 7, 2013, before the expiration date of the '882 patent on August 19, 2014. The terminal disclaimer is submitted solely to confirm that any patent issuing from this application will be enforceable only for and during such period that it and the '882 patent are commonly owned. Applicants respectfully request that, in view of the terminal disclaimer, the rejection of the claims as unpatentable over the '882 patent be withdrawn.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: 1/7/05

By: Elizabeth McNamee
Elizabeth E. McNamee
Reg. No. 54,696

Attachments:

- Terminal Disclaimer;
- Leadbetter, *Clinics in Sports Medicine* 11(2):533,545 (1992);
- Carpal Tunnel Syndrome Information Page from NINDS.

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CELL-MATRIX RESPONSE IN TENDON INJURY

Wayne B. Leadbetter, MD

The cell-matrix response of tendon to sports-induced trauma is characterized by a broad spectrum of histologic and biochemical adaptations to physical load and use. Historically, *tendinitis* has been the clinical term applied to virtually all painful tendon structures, their synovial sheathes, and adjacent bursae. This tradition is challenged by mounting pathologic evidence that distinguishes between the acute traumatic inflammatory response and the more insidious process of chronic tendon degeneration.[27, 71, 106, 108] Although this is by no means a resolved issue, the attempt to distinguish between these two processes bears great importance in prescribing appropriate therapeutic intervention and lies at the crux of the difficulties in predicting successful return to sports performance.[82, 136] There is a significant amount of scientific data on the healing response of acutely traumatized tendon and ligament; however, the literature deals primarily with flexor tendon repaired after laceration in the animal model or human hand. Information on "nontraumatic" injury (i.e., chronic overuse) has been lagging because of the inherent nonoperative nature of the early stages of these conditions and the lack, until recently, of an animal model.[13, 32] This discussion will focus on tissue events at common sites of clinical treatment, such as the rotator cuff tendon complex of the shoulder, the lateral extensor or medial flexor musculature of the forearm and elbow, the patella tendon, and Achilles and posterior tibial tendon. These sites share common attributes of tendons exposed to repetitive high eccentric loads, a muscle tendon unit that in most cases crosses more than one

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joint, and some quality of tenuous vascularity.[2, 19, 33] It is not surprising that such tendons comprise the bulk of treatment requirements and have provided much of the existing biopsy material, such as it is. This article reviews the present understanding of inflammation, repair, and degeneration in tendinopathy. The mechanisms of acute and chronic tendon injury are contrasted and compared. Additionally, the effect of epigenic factors such as age, vascularity, load, use, and rest will be considered. Finally, some theoretic models are provided describing tendon pathophysiology and future therapeutic opportunities. Although some similarities exist in acute trauma,[12, 15] observations will be restricted to tendon tissue response in contradistinction to the myotendinous junction or tendon insertion.

TENDON INJURY, INFLAMMATION, REPAIR, AND DEGENERATION

Sports "injury" (from the Latin *injure*—to make unjust, not right)[124] is the loss of cells or extracellular matrix resulting from sports-induced trauma. Injury represents a failure of cell matrix adaptation to load exposure, whether sudden overload or accumulative overload secondary to cyclic overuse.[83] "Overuse" and "overload" may not be synonymous terms, because injury can result from excessive and rapid change in use without significant change in resistance—hence, the origin of the term "cumulative trauma disorder," or as I prefer "cumulative cell-matrix adaptive response."[8] Synovial structures such as the tendon sheath as well as peritenon structures are prone to this form of stress response.[8, 78, 79] Injuries are divided into acute and chronic patterns according to rate of onset and the mechanism.[126] *Acute* injuries are typified by a sudden crisis followed by a fairly predictable, although often lengthy, resolution. In tendon, an acute injury often consists of midsubstance ruptures occurring either through aberrant tissue or as the result of high strain rates.[4, 19] *Chronic* injury is characterized by slow, insidious onset, implying an antecedent subthreshold spectrum of structural damage leading to a crisis episode that is often heralded by pain and/or signs of inflammation. Chronic injury may last months or even years and is distinguished by a persistence of symptoms without resolution. Paratenonitis and tendinitis are typical of such complaints. There appears to be some overlap between acute and chronic injuries, with the bridging stage at 4 to 6 weeks termed the "subacute stage" of injury.[73]

It is difficult to define sports injury clinically. Furthermore, because tendon injury falls within the domain of an athletic soft-tissue complaint, the athletes' injury is often defined solely by the amount of pain and the inability to perform. Noyes et al[103] have directed attention to this inadequacy and to the importance of defining the exact anatomic extent and occurrence of tissue injury. Classic signs of inflammation after injury are *not* always present or identifiable.[136] The complaint is not so much identified with specific structure as within an anatomic area. It is a "painful shoulder," not a painful biceps tendon; it is a

"painful knee," not a painful patella tendon. And although the immediate onus on the examiner is to be competent and accurate in making the physical diagnosis, the elicitation of pain does not necessarily shed light on the exact pathology or mechanism of injury. Hence, tendon injury relating to occult joint instability or dynamic tendon stress overload as may be present with the hyperpronating foot may be revealed only by further analysis.

Rovere's attempt to define tendinitis in a study of theatrical dance students exemplifies this difficulty. He defined tendinitis as "a syndrome of pain and tenderness localized over a tendon, usually aggravated by activities that bring the particular muscle tendon unit into play, usually against resistance. . . . The syndrome is inclusive of tenosynovitis and tenovaginitis as well as actual inflammation of the tendon substance itself."[83]

"Sports-induced inflammation" (from the Latin *inflammare*, to set on fire)[123] is a localized tissue response initiated by injury or destruction of *vascularized* tissues exposed to excessive mechanical load or use. It is a time-dependent evolving process characterized by vascular, chemical, and cellular events leading to tissue repair, regeneration, or scar formation. Clinically observed pathways of sports-induced soft-tissue inflammation include spontaneous resolution, fibroproductive healing, regeneration, or chronic inflammatory response (Fig. 1). The four cardinal signs of acute inflammation were defined by Celsus (AD 14–37) in the often quoted phrase: *"rubor et tumor cum calore et dolore"* (redness and swelling with heat and pain) (Table 1). It is important to note that this was likely a description of an empyema and fistula of the chest.[82] Based on historic tradition, pain has assumed a disproportionate role in the definition of inflammation, such that any painful structure is immediately presumed inflamed. It has taken the advent of more accurate noninvasive assessment such as magnetic resonance imaging and the accumulation of surgical biopsy evidence to correct what may be a clinical misinterpretation.[26, 71, 72, 108] As will be further discussed, the source of connective tissue pain in now known to be multifactorial.[51]

Repair of soft-tissue injury has been defined as replacement of damaged or lost cells and extracellular matrices with new cells and matrices.[138] Regeneration is a form of repair that produces new tissue that is structurally and functionally *identical* to normal tissue. Repair by scar is the postnatal mammalian response to injury, unlike in the fetal wound, which is capable of healing without exuberant scar formation.[1, 94] This is especially true in a stable tissue (less than 1.5% mitotic activity) as opposed to a labile tissue such as liver.[92] Jennings and Hunt[63] note "in the post-natal animal, the cellular response to achieve tissue integrity by scar formation after injury overrides the potential for perfect regeneration and return of all function, placing importance on early recovery free of infection; [however] perhaps the ability to regenerate tissue is not lost but is subdued by the necessity for survival." Such observations are the underpinning of the present interest in cell mediators to modulate healing response.

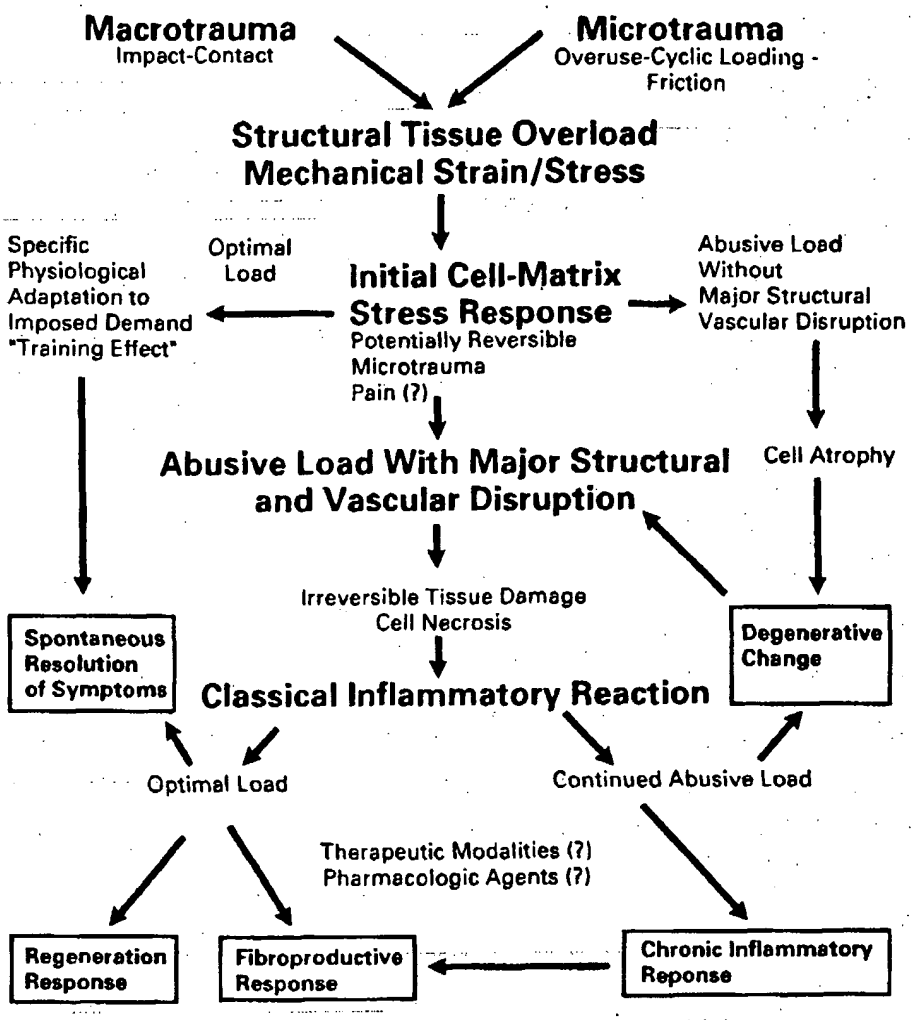

Figure 1. Schema of the theoretical pathways of sports-induced inflammatory response. (*From* Leadbetter WB: An introduction to sports-induced inflammation. *In* Leadbetter WB, Buckwalter JB, Gordon SL (eds): Sports-Induced Inflammation: Clinical and Basic Science Concepts. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1990, p 2; with permission.)

Degeneration describes a change in tissue from a higher to a lower or less functionally active form.[82] Such weakened structures are then more vulnerable to sudden dynamic overload or cyclic overloading leading to mechanical fatigue and failure. A prominent source of degeneration is cell atrophy, which is the decrease in the size and/or function of a cell in response to a presence (or lack of) an environmental signal.[115] Such down-regulation involves decreased protein synthesis and a decrease in such activities as energy production, replication, storage, and contractility. In sports injury, immobilization is a prominent cause of cell atrophy in tendon.[41, 45, 114, 140] Additional causes include decreased nutrition, diminished endocrine hormonal influence, persistent inflammation, aging, and denervation (Fig. 2). Reversal of the degenerative process is not a typical feature in degenerative conditions

Table 1. RECOGNITION OF THE "CARDINAL SIGNS" OF INFLAMMATION

Heat, *Calor*—metabolic radiant energy
Redness, *Rubor*—increased vascularity (angiogenesis) and blood flow
Swelling, *Tumor*—extracellular edema and matrix changes
Pain, *Dolor*—stimulation of afferent nerve endings by noxious mediators
Loss of function,* *Functi laesa*—decreased performance caused by direct damage or inhibiting pain, edema

*First pronounced by Virchow.[131]

beyond an undefined cell matrix limit.[136] Ultimately, degeneration represents a profound imbalance in cell matrix homeostasis.

Chronic inflammation involves the replacement of leukocytes by macrophages, plasma cells, and lymphocytes in a highly vascularized

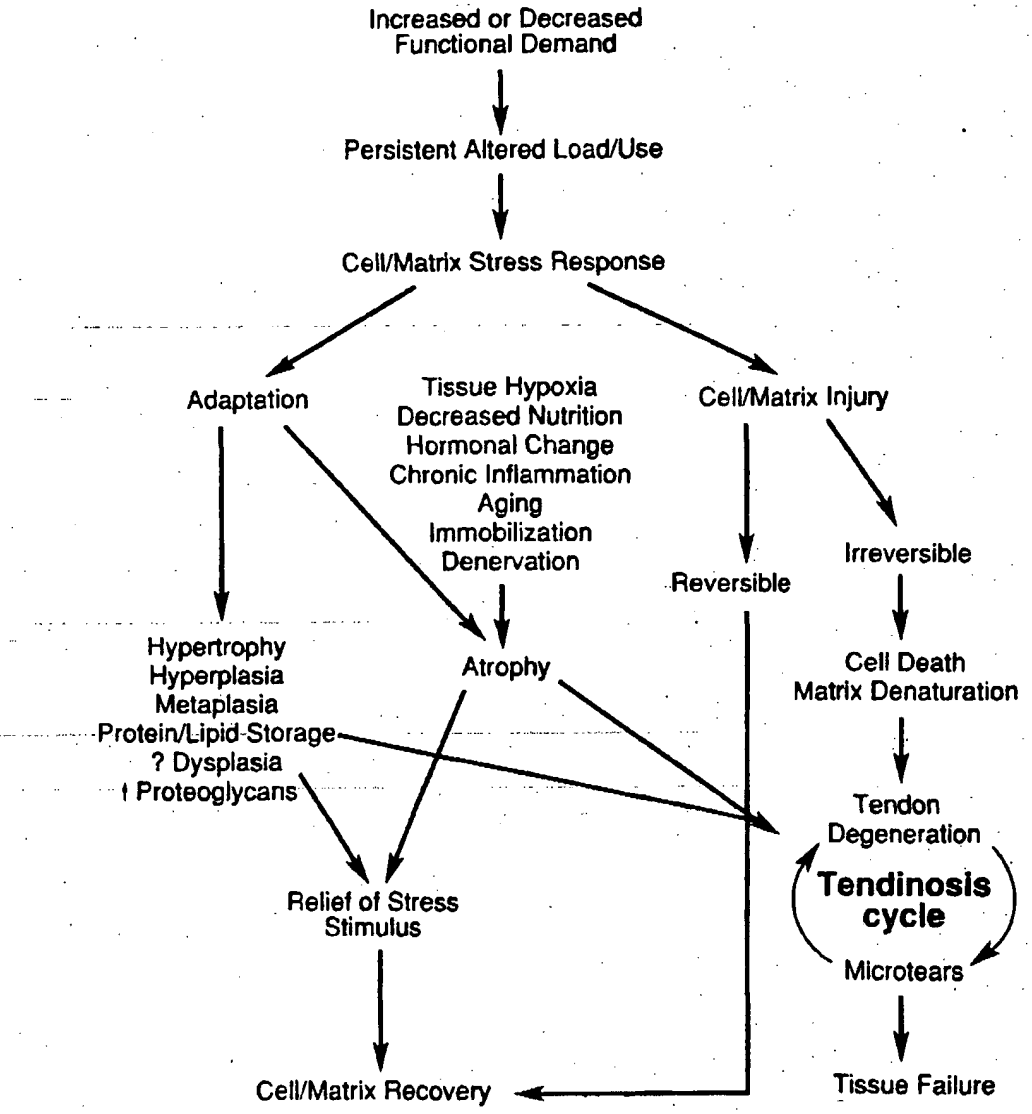

Figure 2. Cell matrix response to change in functional level. In this model, tendinosis results from a failed cell matrix adaptation to excessive changes in load use. Such failure is modified by both intrinsic and extrinsic factors.

and innervated loose connective-tissue milieu at the site of injury.[10, 84, 100, 114] Although findings of chronic inflammation are typical in sites such as the lateral epicondylar lesions of the elbow,[100] such responses are not found in all chronic sports injuries.[70] The mechanism that converts an acute inflammation to a chronic inflammatory process is not known; continued abusive load and irritation may stimulate the local release of cytokines, resulting in both autocrine (cell self-stimulation) and paracrine (stimulation of adjacent cells) modulation of further cell activity.[3, 10, 29, 34, 47]

Inflammation, degeneration, and repair form a functional spectrum of cell matrix responses with predominance of any one response depending on the mechanism of injury and the homeostatic balance of the tendon tissue.

TENDON INJURY RESPONSE

All sports-related connective tissue injury response occurs in the context of two interrelated categories: (1) macrotraumatic—acute tissue destruction; and (2) microtraumatic—chronic abusive load or use.

In tendon, the mechanism of injury has much to do with the subsequent pathohistologic pattern.

Acute Macrotraumatic Tendon Injury Response

Acute tissue loss or damage results in regeneration, fiber-productive response and repair by scar tissue, or some combination of both.[56, 63] Factors that contribute to the evolution of chronic inflammation or degenerative change are less understood.[56] The moment of tissue injury is defined by the onset of vascular disruption and the initiation of the clotting mechanism and platelet activation. A cascade of overlapping processes that has been described as "predictable" includes (1) inflammation, (2) cell replication, (3) angiogenesis, (4) matrix deposition, (5) collagen protein formation, (6) contraction, i.e., remodeling, and, in the case of exposed wounds, (7) epithelization (Fig. 3). In fact, this represents an ideal sequence of events influenced by not only the type of insult but also such facts as age, vascularity, nutrition, genetics, hormonal changes, innervation, and activity level. The literature contains many excellent and exhaustive reviews of the vascular cellular and biochemical events in this process.[1, 5, 15, 18, 25, 29, 34, 40, 44, 55, 56, 62, 89, 105, 114, 129, 138] Acute connective-tissue injury has been further classified into three phases.[73, 83, 104]

Phase 1: Acute vascular-inflammatory response. After wounding, the first reparative "cells" to appear in most vascularized wounds are platelets, which are a prominent source of cell mediators such as platelet-derived growth factor (PDGF), platelet factor 4, insulin-like growth factor 1 (IGF-1), transforming growth factor (TGF-β1 and β2), and an uncharacterized chemotractant to endothelial cells.[57] Activation of the coagulation cascade and formation of a fibrin clot containing fibronectin with crosslinking to collagen is vital to facilitate reparative

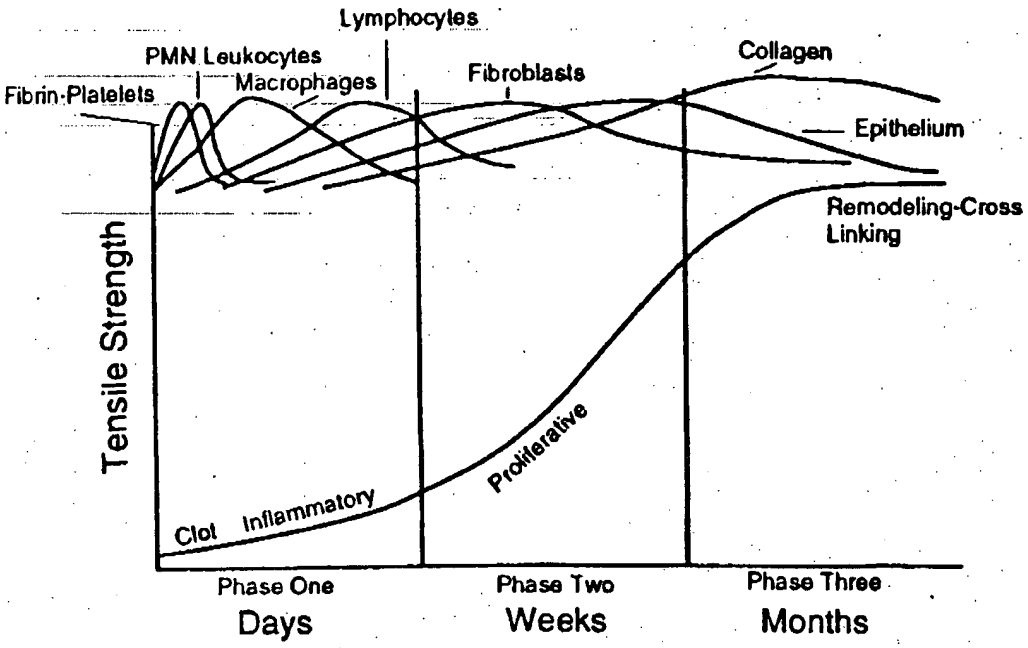

Figure 3. Ideal wound healing model. Originally derived from the study of skin lacerations, a variety of factors may distort the actual healing sequence in tendon. Although this diagram is an accurate portrayal of cell matrix wound healing events, note that the temporal relationship of the various phases is such that the duration of phase one is measured in hours or a few days, but phase three may extend indefinitely. Normal tendon is not regenerated, however. PMN = polymorphonuclear cell. (*Adapted from* Gamble JG: The musculoskeletal system: Physiological basics. *In* Hunter-Griffin L (ed): Athletic Training and Sports Medicine, ed 2. New York, Raven Press, 1988, p 105; with permission.)

cell activity. Fibronectins are a class of noncollagenous glycoproteins that act as adhesive molecules, integrating the extracellular matrix. Hyaluronate, a high-molecular-weight matrix glycosaminoglycan, interacts with fibronectin to create a scaffold for cell migration; later, its degradation by neutrophil hyaluronidases to a smaller molecular form stimulates the angiogenesis that will support fibroblast activity. There are three major consequences of the inflammatory phase: (1) some initial wound strength is provided by crosslinking a fibronectin in collagen; (2) damage tissue from the initial trauma is removed; (3) and endothelial sites and fibroblasts are recruited and stimulated to divide.[91] During this phase, release of complement activates polymorphonuclear cell migration into the extravascular space, providing for the removal of cellular debris and initiating chemotaxis of additional inflammatory cells including the tissue macrophage. In tendon, these phagocytic cells may derive from differentiation of epitenon fibroblasts.[90] Granules within these leukocytes release hydrolytic enzymes that hydrolyze cell membrane phospholipids, producing arachidonic acid, metabolites, cytokines, proteases, and oxidants (Fig. 4). The resulting *arachidonic acid cascade* is an enzymatically driven sequence, leading to the production of prostaglandins, thromboxanes, leukotrienes, eicosanoids, and slow reacting substance of anaphylaxis (SRS-A)[115] (Fig. 5). This cascade is the primary chemical event producing the cardinal signs of inflammation. Initiating in minutes, this phase lasts for essentially as long as the

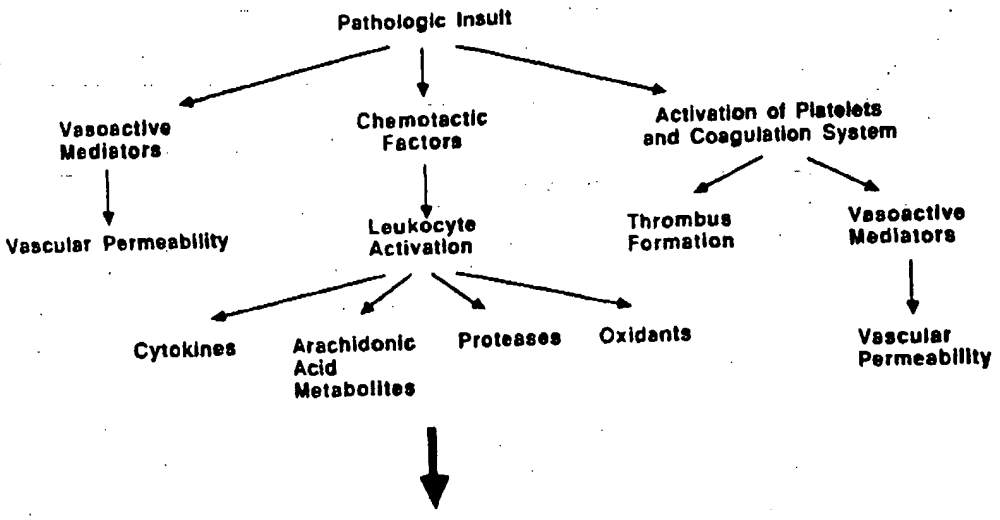

Figure 4. Mediators of the inflammatory response. (*From* Fantone JC: Basic concepts in inflammation. *In* Leadbetter WB, Buckwalter JB, Gordon SL (eds): Sports-Induced Inflammation: Clinical and Basic Science Concepts. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1990; with permission.)

body requires to set the stage for repair.[7] Assuming no coincident infection or repetitive disturbance to the wound, this is usually a matter of 3 to 5 days.

Phase 2: Repair-regeneration. Beginning at 48 hours and lasting up to 6 to 8 weeks, this phase is characterized by the presence of the tissue macrophage, formally a circulating monocyte. This pleuripotential cell is the starship of wound repair and is capable of directing essentially the complete sequence of events in this proliferative phase. The macrophage is characteristically mobile, capable of releasing a wide menu of growth factors, chemotractants, and proteolytic enzymes when appropriate or necessary for the activation of fibroblasts and tendon repair. The reparative cell in tendon injury is the tenocyte, which when activated behaves like a modified form of fibroblast or fibrocyte. This cell is the source of collagen production, protein mediators of repair, and matrix proteoglycans. Tenocytes are classified as stable cells, meaning less than 1.5% are mitotically active at any one time.[91] The cells have a low respiratory quotient and a low rate of collagen turnover.[28, 47] Bound normally within a dense, linear-oriented collagenous matrix, these cells take on a distinct biologic behavior and a fibroproductive phenotypic expression dictated in part by their deformation and cell shape.[4] Initially, type III collagen in a woven pattern is rapidly deposited. Type III collagen is characterized by a small fibril that is deficient in crosslinking. The remainder of the repair process is characterized by shift to the deposition of type I collagen, which continues for an indeterminate period in the final maturation phase.[45] The critical, driving force in this stage of the wounding response is a relative hypoxia in the wound micro environment and rising lactate

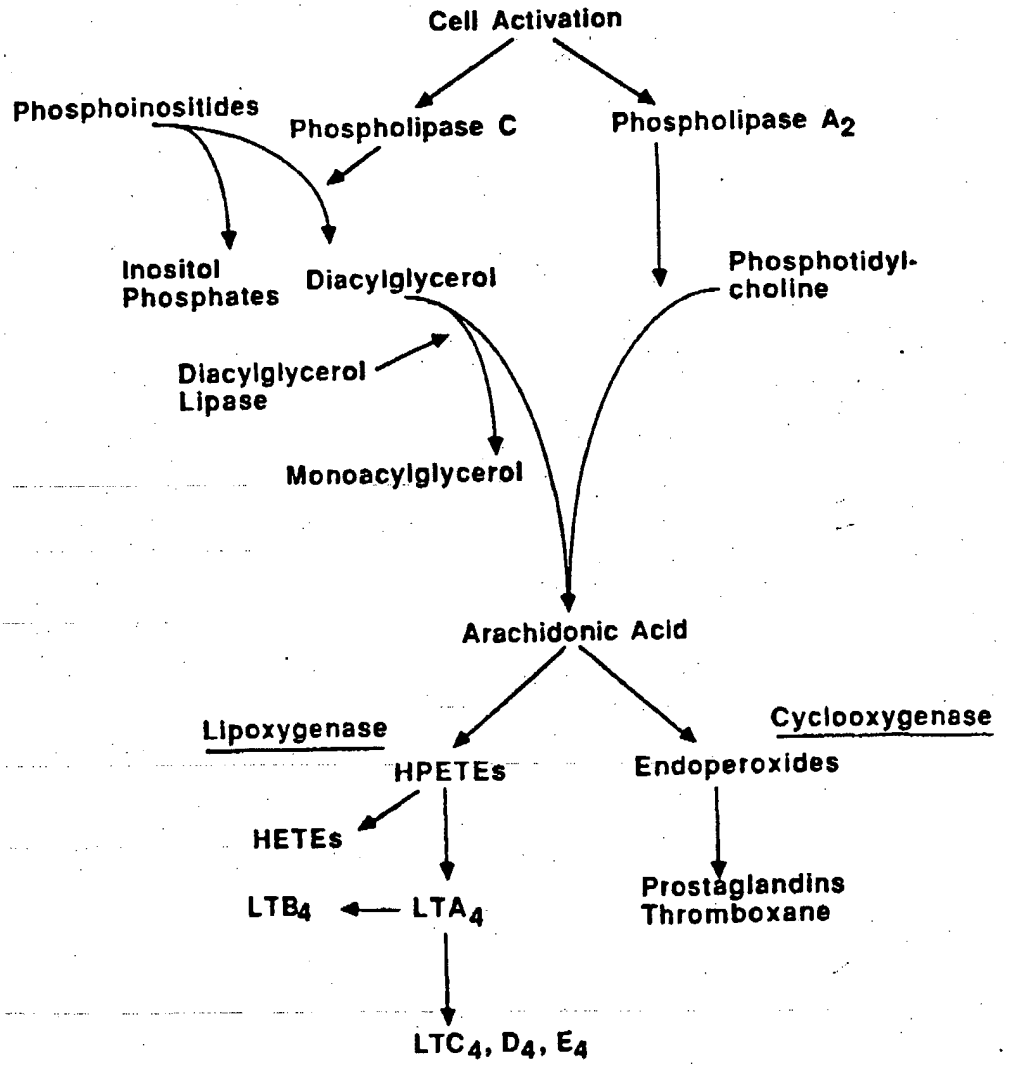

Figure 5. Generation of arachidonic acid metabolites. HETEs = hydro-oxyecoia tetranoic acids; HPETEs = hydro-peroxyecoiatetranoic acid compounds; LT = leukotriene. (*From* Fantone JC: Basic concepts in inflammation. *In* Leadbetter WB, Buckwalter JB, Gordon SL (eds): Sports-Induced Inflammation: Clinical and Basic Science Concepts. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1990; with permission.)

levels contributed in part by the release of large amounts of lactate by the tissue macrophage.[57]

Phase 3: The remodeling maturation phase. This is characterized by a trend toward decreased cellularity and an accompanying decrease in synthetic activity, increased organization of extracellular matrix, and a more normal biochemical profile.[80] Collagen maturation and functional linear realignment are usually seen by 2 months after injury. In the lacerated flexor tendon, by approximately 4 months after injury there appears to be complete maturation of the repair site, and the fibroblasts revert to quiescent tenocytes. Final biomechanical properties can be reduced by as much as 30% despite this remodeling effort.[4, 33, 45, 46] Biochemical differences in collagen type and arrangement, water content, DNA content, and glycosaminoglycan content persist indefinitely, and the material properties of these scars never equal those of the intact tendon[4] (Fig. 6).

Cellular response after tendon laceration may assume two patterns: (1) an extrinsic, callus-like response with proliferation and bridging of the injury by the epitenon cells,[12, 116] or (2) an intrinsic healing response as the result of endotendon fibroblast repair.[87, 90] In tendons with a well-developed synovial sheath, wounds producing an accompanying vascular insult such as laceration, crush, avulsion, or rupture will heal by an extrinsic dominant pattern.[46] This is evidenced by the resulting scar and formation of adhesions.[66] Excessive fibrosis, its mediation, and its modulation have become the focus of current orthopedic therapy. Passive mobilization and controlled use of load have shown promise in improving tendon and ligament healing.[125, 134] Studies suggesting the inflammatory response is nonessential and that tendons do possess an intrinsic capacity to heal have direct implications for the biologic potential for cell matrix response in the microtraumatized tendon. Although epitenocyte is actively involved in repair of macrotraumatic lesions, the role of the endotenocyte remains controversial.[12, 87]

Chronic Microtraumatic Tendon Injury

Microtraumatic tendon injury is distinguished by the observation that degenerative changes are a histologic feature, especially in cases of spontaneous tendon rupture.[6, 14] This degenerative tendinopathy is thought to be the result of a hypoxic degenerative process involving both tenocyte and matrix components.[70, 71, 76, 77] Inflammatory cell infiltration and orderly phased wound repair as seen in macrotrauma seem to be absent or aborted. Although much of the histologic evidence for degenerative tendinopathy has been derived from the treatment of spontaneous Achilles tendon rupture,[6, 26, 27, 30, 71, 77, 78, 81, 108] Kannus et al,[71] in a recently published study of the histopathologic changes preceding spontaneous rupture of tendon in 891 patients (397 Achilles tendons, 302 biceps brachii tendons, 40 extensor pollicis longus tendons, 82 quadriceps tendons and patellar ligaments, and 70 other tendons), found 97% were affected with prior pathologic change. The mean patient age was 49 years. Of interest was the finding of similar pathologic changes in 34% of the otherwise asymptomatic control

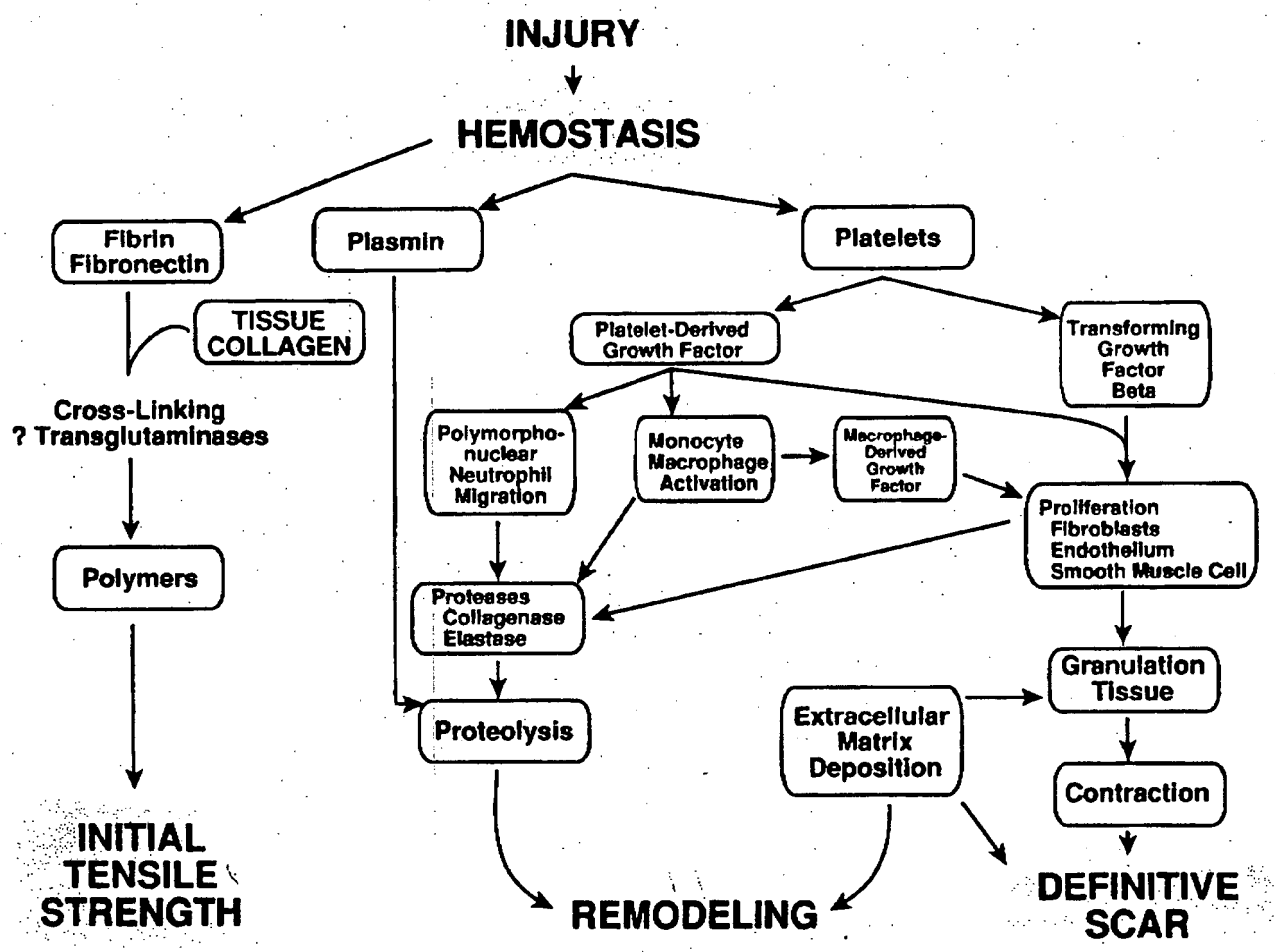

Figure 6. Summary of events in macrotraumatic wound response. (*From* Martinez-Hernandez A: Basic concepts in wound healing. *In* Leadbetter WB, Buckwalter JB, Gordon SL (eds): Sports-Induced Inflammation: Clinical and Basic Science Concepts. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1990, p 78; with permission.)

population. Similar observations by Puddu et al[108] and Clancy[27] have led to the definition of a new classification of tendon injury and to the coining of the term "tendinosis": a focal area of intratendinous degeneration that is initially asymptomatic. There has been no convincing evidence for the existence of this form of microtrauma response in the young athlete; however, the profound exposure in youth endurance sports and the prevalence of complaints bear further investigation. Based upon the anatomy of the tendon and its surrounding tissues, it is possible to describe four pathologic conditions (Table 2). This classification emphasizes the distinction between peritenon or synovial inflammation and increasing involvement of the tendons' substance as a likely reflection of failed adaptation to physical load and use, and emphasizes the variable stress responses of tendon structure. Similar pathology has been found in patella tendinosis.[9, 14, 39]

Blackman et al[13] have provided recent experimental model evidence in the rabbit for the existence of chronic Achilles paratenonitis with tendinosis, with light microscopic examination revealing degenerative changes in the tendon and increased number of capillaries, infiltrates of inflammatory cells, edema, and fibrosis in the peritenon. Leadbetter[85] has reported similar findings in the adult athlete with overuse tendon injury requiring surgical treatment. Specimens included Achilles tendon, posterior tibial tendon, digital finger flexor tendon, lateral elbow extensors, medial elbow flexor, patella tendon, and triceps. All specimens displayed varying degrees of the following: (1) tenocyte hyperplasia; (2) a blastlike change in morphology from normal tenocyte appearance; (3) prominent small vessel in-growth with accompanying mesenchymal cells; (4) paravascular collections of histiocytic or macrophagelike cells[18]; (5) endothelial hyperplasia and microvascular thrombosis; (6) collagen fiber disorganization with mixed reparation and degenerative change; (7) microtears and collagen fiber separations (Figs. 7 to 12). Inflammatory cell populations were prominent in the synovium and peritendinous structures (Fig. 13), as well as the surrounding areas of intratendinous calcification, and at sites of previous intratendinous steroid injection. Reparative cells were evident in patients with tendinosis and tendinitis pathology despite the coexistent findings of cell matrix degeneration. Polymorphonuclear cells and lymphocytes were minimally present.

The synovial sheath and paratenon is also involved in microtraumatic injury, especially as the result of friction with excitation of the synovial cells. Kvist et al[77] studied 16 athletes presenting with peritendinitis. Increased enzyme activities were mainly found in the fibroblast, inflammatory cells, and vascular walls in the peritenon. The results indicated marked metabolic changes occur with an increased catabolism, lowered pH, and decreased oxygenation of the inflamed areas. Typical findings include fibroexudation with deposition of fibronectin and fibrinogen, proliferation of blood vessels, and in some cases marked endothelial hyperplasia with obliteration of microarterioles. Growth factors have been substantiated to modulate this process[64–66, 69] (Figs. 14 and 15).

Table 2. TERMINOLOGY OF TENDON INJURY

New	Old	Definition	Histologic Findings	Clinical Signs and Symptoms
Paratenonitis	Tenosynovitis Tenovaginitis Peritendinitis	An inflammation of only the paratenon, either lined by synovium or not	Inflammatory cells in paratenon or peritendinous areolar tissue	Cardinal inflammatory signs: swelling, pain, crepitation, local tenderness, warmth, dysfunction
Paratenonitis with tendinosis	Tendinitis	Paratenon inflammation associated with intratendinosis degeneration	Same as I, with loss of tendon collagen fiber disorientation, scattered vascular ingrowth but no prominent intratendinous inflammation	Same as I, with often palpable tendon nodule, swelling, and inflammatory signs
Tendinosis	Tendinitis	Intratendinous degeneration due to atrophy (aging, microtrauma, vascular compromise, etc.)	Noninflammatory intratendinous collagen degeneration with fiber disorientation, hypocellularity, scattered vascular ingrowth, occasional local necrosis or calcification	Often palpable tendon nodule that can be *asymptomatic*, but may also be point tender. Swelling of tendon sheath is absent
Tendinitis	Tendon strain or tear A. Acute (less than 2 weeks) B. Subacute (4–6 weeks) C. Chronic (over 6 weeks)	Symptomatic degeneration of the tendon with vascular disruption and inflammatory repair response	Three recognized subgroups: each displays variable histology from purely inflammation with acute hemorrhage and tear, to inflammation superimposed upon pre-existing degeneration, to calcification and tendinosis changes in chronic conditions. In chronic stage there may be: 1. Interstitial microinjury 2. Central tendon necrosis 3. Frank partial rupture 4. Acute complete rupture	Symptoms are inflammatory and proportional to vascular disruption, hematoma, or atrophy-related cell necrosis. Symptom duration defines each subgroup:

Data from Clancy WG: Tendon trauma and overuse injuries. *In* Leadbetter WB, Buckwalter JA, Gordon SL, (eds): Sports-Induced Inflammation. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1990; and Puddu G, Ippolito E, Postacchini P: A classification of Achilles tendon disease. Am J Sports Med 4:145–150, 1976.

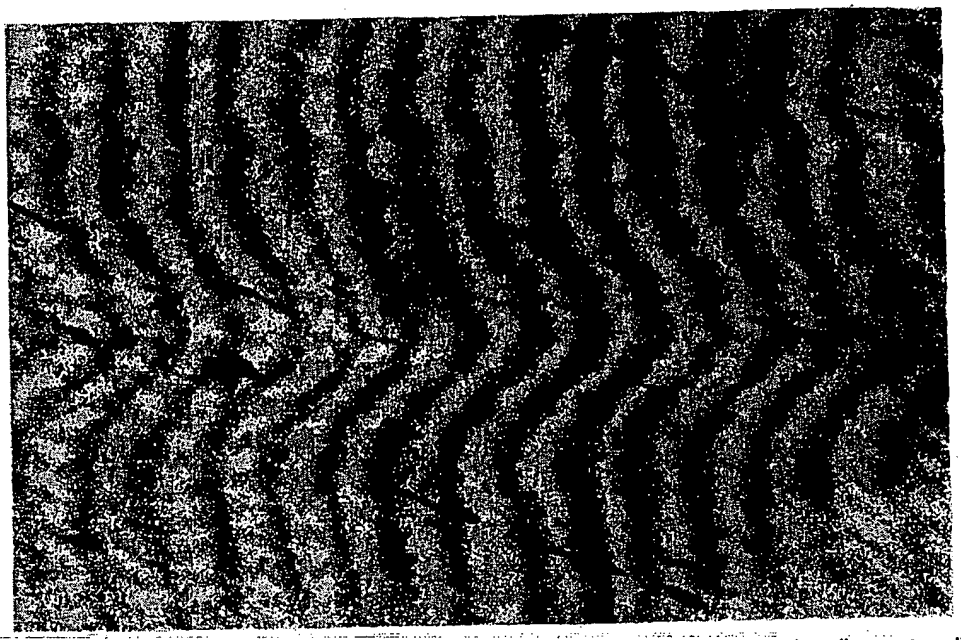

Figure 7. Normal Achilles tendon. Note the linear cell shape and orientation (hematoxylin-eosin, × 162.5).

Figure 8. Achilles tendinosis. Note the tenocyte hyperplasia, cell vacuolation, and blast-like change in morphology characteristic of the stress-responsive tenocyte (i.e., tendon fibroblast) (hematoxylin-eosin, × 260).

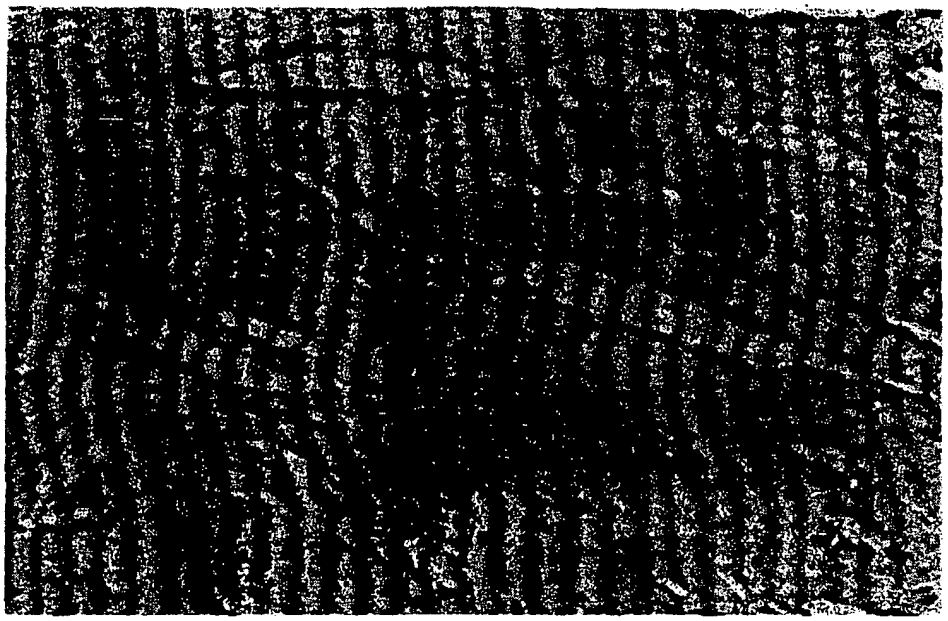

Figure 9. Achilles tendinosis. Note prominent small vessel ingrowth and angioneogenesis (hematoxylin-eosin, × 162.5).

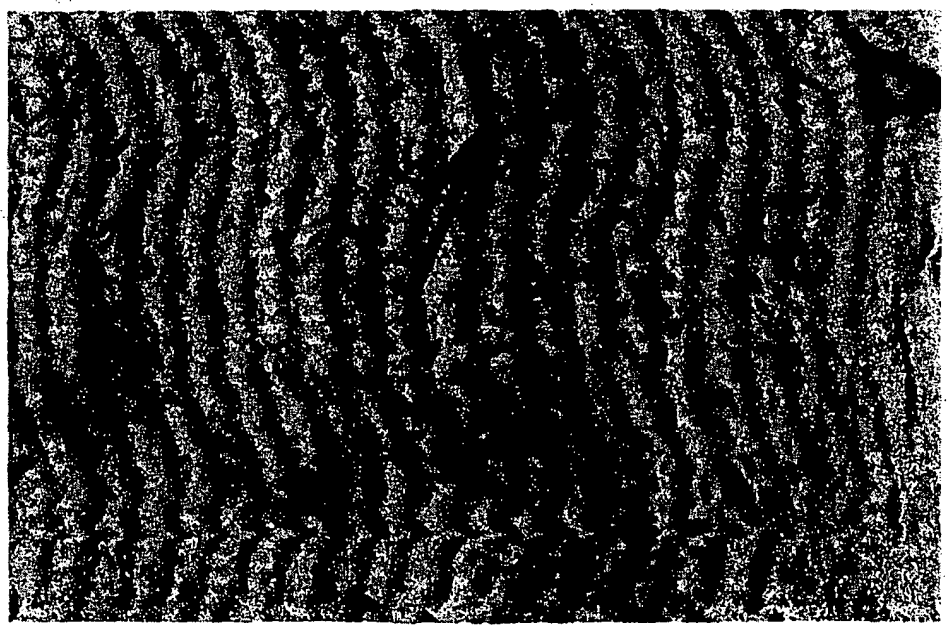

Figure 10. Achilles tendinosis. Endothelial hyperplasia and microvascular thrombosis (hematoxylin-eosin, × 162.5).

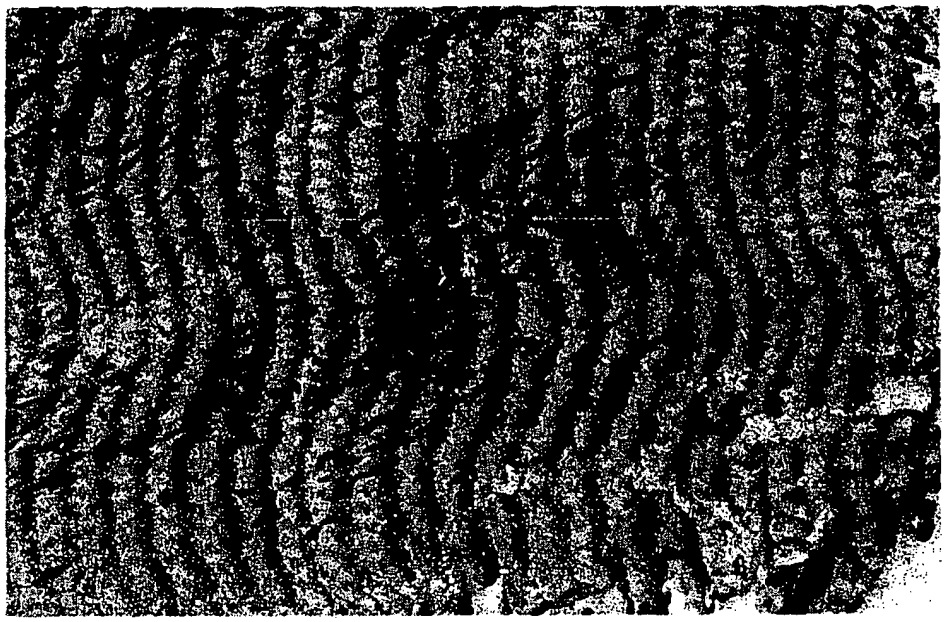

Figure 11. Achilles tendinosis. Collagen fiber disorganization with coexistent repair and degenerative change (hematoxylin-eosin, × 162.5).

Badalamente et al, [8, 9] in studying the biopsy tissues of typical cumulative trauma disorders including trigger-finger, de Quervain's disease, and carpal tunnel syndrome, identified fibrocartilaginous metaplasia in the trigger-finger and de Quervain's condition but not a

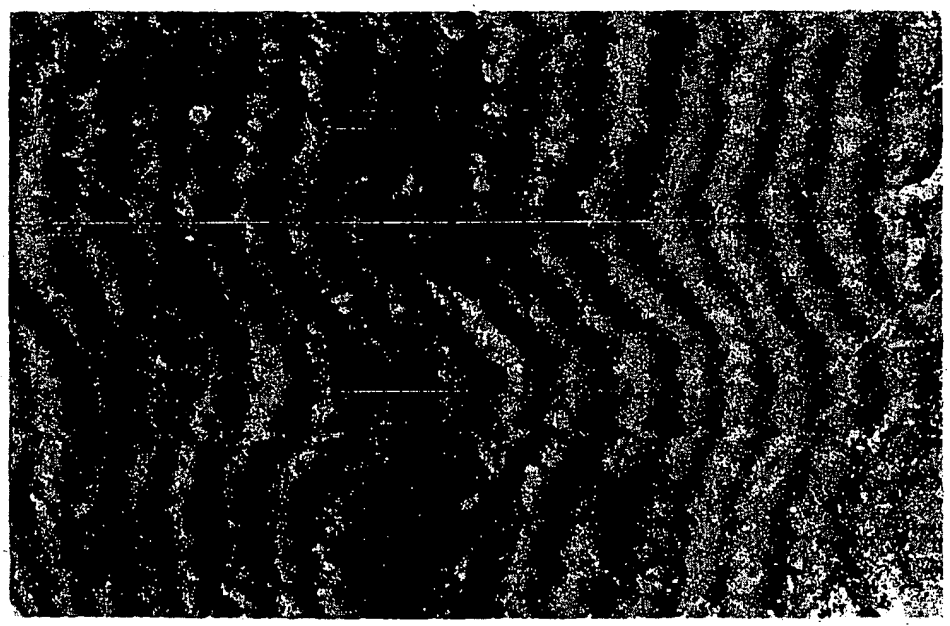

Figure 12. Achilles tendinosis; hyalin degeneration (hematoxylin-eosin, × 162.5).

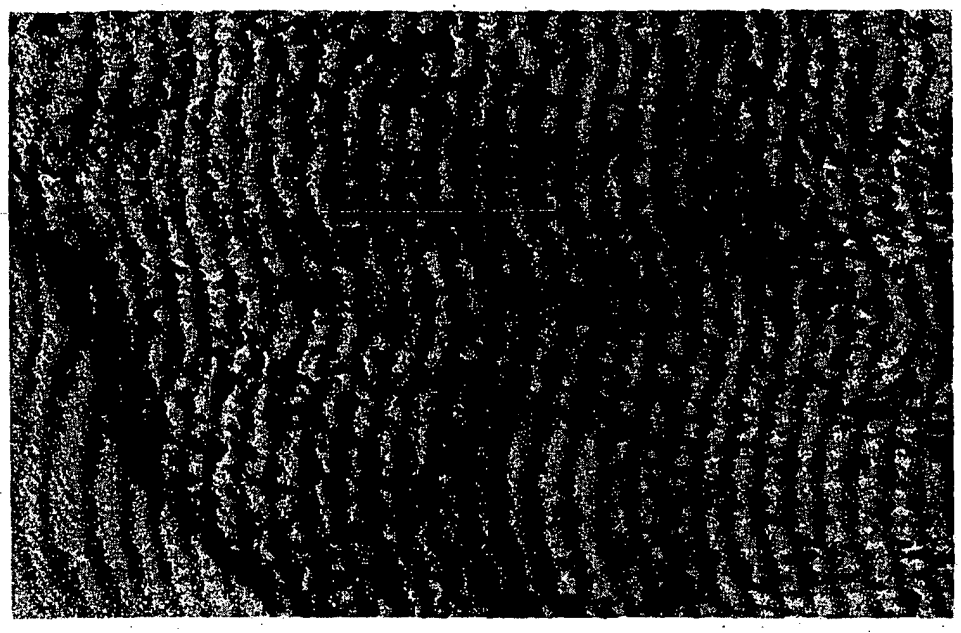

Figure 13. Paratenonitis of a digital flexor tendon of the hand. Note the prominent inflammatory cells with synovial hyperplasia (hematoxylin-eosin, × 162.5).

synovitis. A chondroid metaplasia stress response appeared to be present. Leadbetter found both chondroid metaplasia in the pulley A1 tissue as well as synovitis in the tenosynovium[85] (see Fig. 13). In carpal tunnel syndrome, a proliferation of the type B secretory synovial cell

Figure 14. Achilles paratenonitis with tendinosis. Note the synovial hyperplasia with peritenon adhesions and tendon swelling.

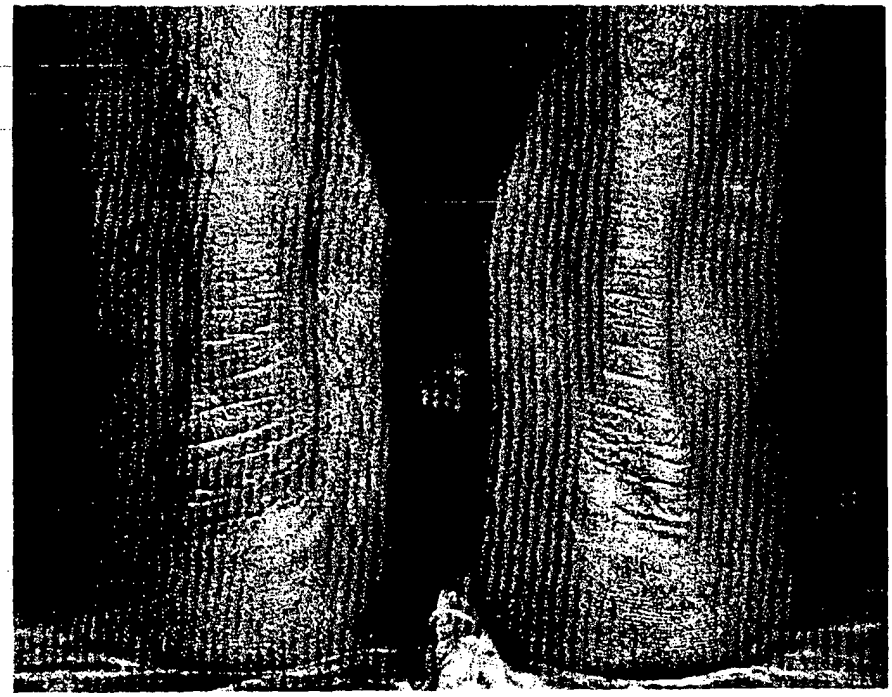

Figure 15. Clinical appearance of Achilles paratenonitis of the left heel (note tenovagium thickening).

in the tendon sheath was found.[8] Almekinders et al[3] have demonstrated an in vitro capability of the human internal tendon fibroblast to produce inflammatory mediators including prostaglandin E_2 and leukotriene (LTB4) in response to repetitive motion.

In flat tendons, such as the extensor carpi radialis brevis of the lateral elbow, there are similar findings of intratendinous degeneration with a gray immature edematous and friable scar tissue.[101] This tissue is essentially characteristic in appearance of chronic granulation tissues seen in various tendon sites throughout the body. It has the additional characteristic of many small fiber sensory nerves and presumably high concentration of nociceptor stimulators (Fig. 16).

The electronic microscopic appearance of microtraumatic tendon degeneration reveals alterations in the size and shape of mitochondria in the nuclei of the tenocyte. Intracytoplasmic or mitrochondrial calcification may be seen.[135] Dystrophic calcium pyrophosphate salts precipitate indegenerative tendon tissue as a result of mitrochondrial injury.[115] The resulting calcification is deposited in the collagen matrix as chalky-appearing hydroxypepityte crystals, the "tombstones" of tendon injury. Cytoplasmic vacuoles, lipid deposition, and cell necrosis changes are thought to result from relative hypoxia.[71] Similar changes have been documented in reparative cells, however, after tendon laceration.[90] Changes in the collagen fibers include longitudinal splitting, disintegra-

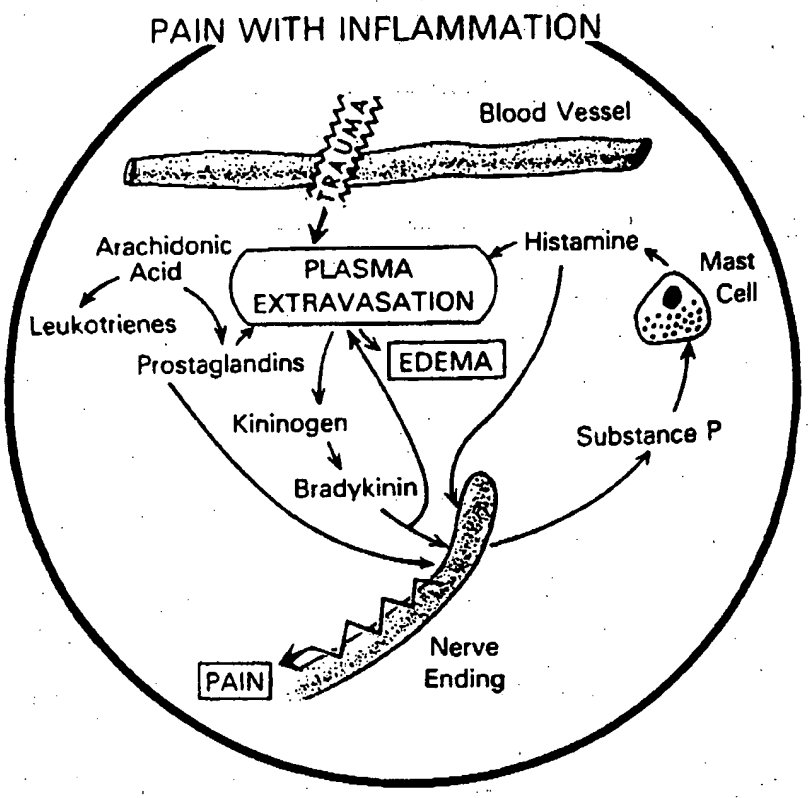

Figure 16. Schema of the positive-feedback relationship that develops during the course of inflammation secondary to sports-related injuries. (*From* Hargreaves KM, Troullos ES, Dionne RA: Pharmacologic rationale for the treatment of acute pain. Dent Clin North Am 31:675–694, 1987.)

tion, angulation with a unique bent-fiber appearance (knicking), and abnormal variation in fiber diameter.[71, 128]

Two cases from our experience are illustrative. Case 1 is a 42-year-old male jogger found to have an Achilles tendinosis lesion requiring surgery. Biopsy several centimeters proximal to the clinical lesion demonstrated a normal tenocyte linear appearance with fairly normal organelle configurations; however, there is borderline mitochondrial swelling and some variation in collagen fibril size (Fig. 17). The matrix changes seen in this case are also consistent with some quality of aging.[122, 127] In the same case, at the site of the lesion, fibroblastic activity is aggressive, with pronounced rough endoplasmic reticulum with cisternae dilated with electron-dense material, implying proteoglycan and protein production (Fig. 18). There is pronounced collagen fibril production of variable orientation and size (Fig. 19). Thus, although degeneration has been implicated in tendinosis, some cells still are metabolically active. This suggests a dysfunction of tendon tissue maintenance influenced by environmental factors that are to be further defined. Case 2 (Fig. 20) reveals severe cell stress response as evidenced by prominent lipid storage and even the presence of cholesterol clefts with cell death[118] (Fig. 21). It is interesting to note the variability in

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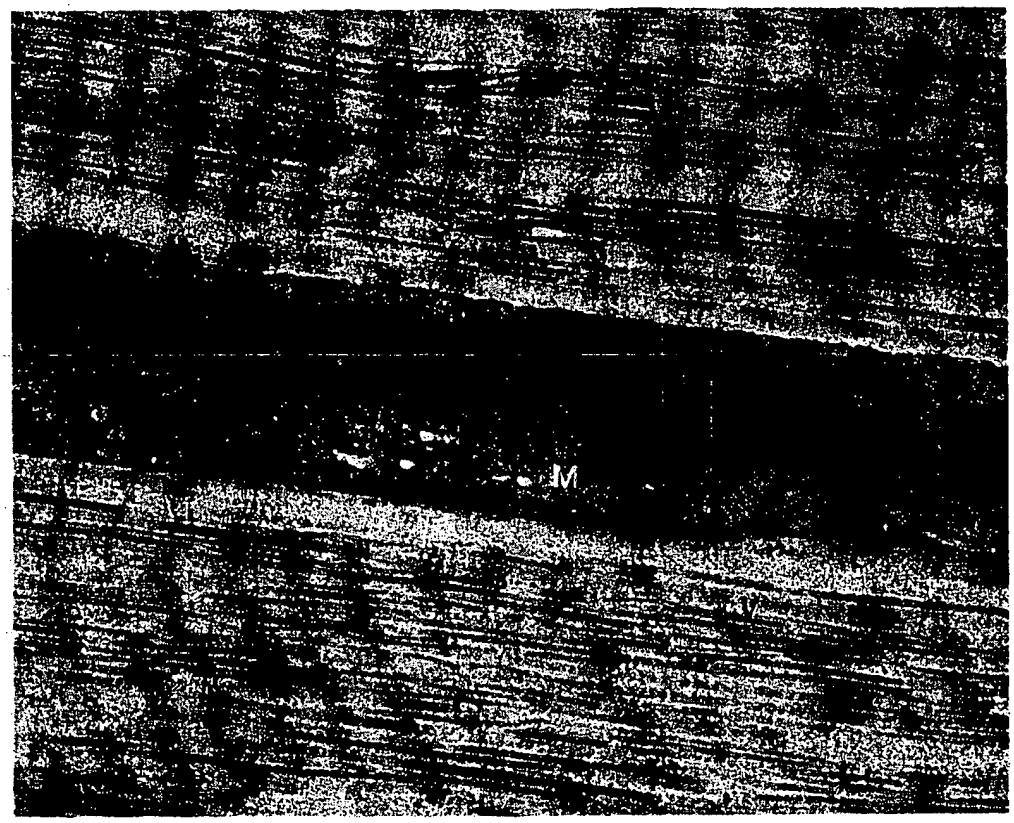

Figure 17. Transmission electron micrograph from control biopsy site in Achilles tendon. Note subtle mitochondrial (M) swelling with age-dependent variability in collagen fibril size (V) (osmium, original magnification × 38,000).

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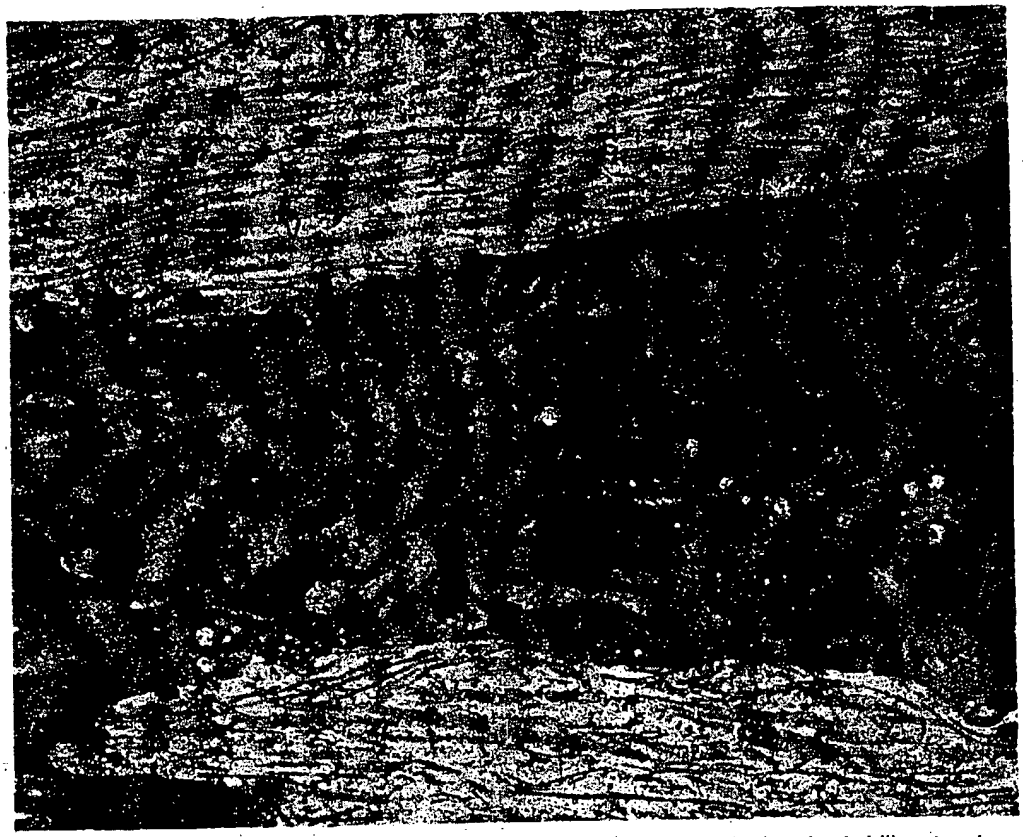

Figure 18. Transmission electron micrograph from tendinosis lesion in Achilles tendon. Note prominent rough endoplasmic reticulum with associated ribosomes and prominent swelling secondary to presumed proteoglycan deposition (ER ↑), mitochondria with cisternal damage (M), and variable collagen fibril production (V) (osmium, original magnification × 29,250).

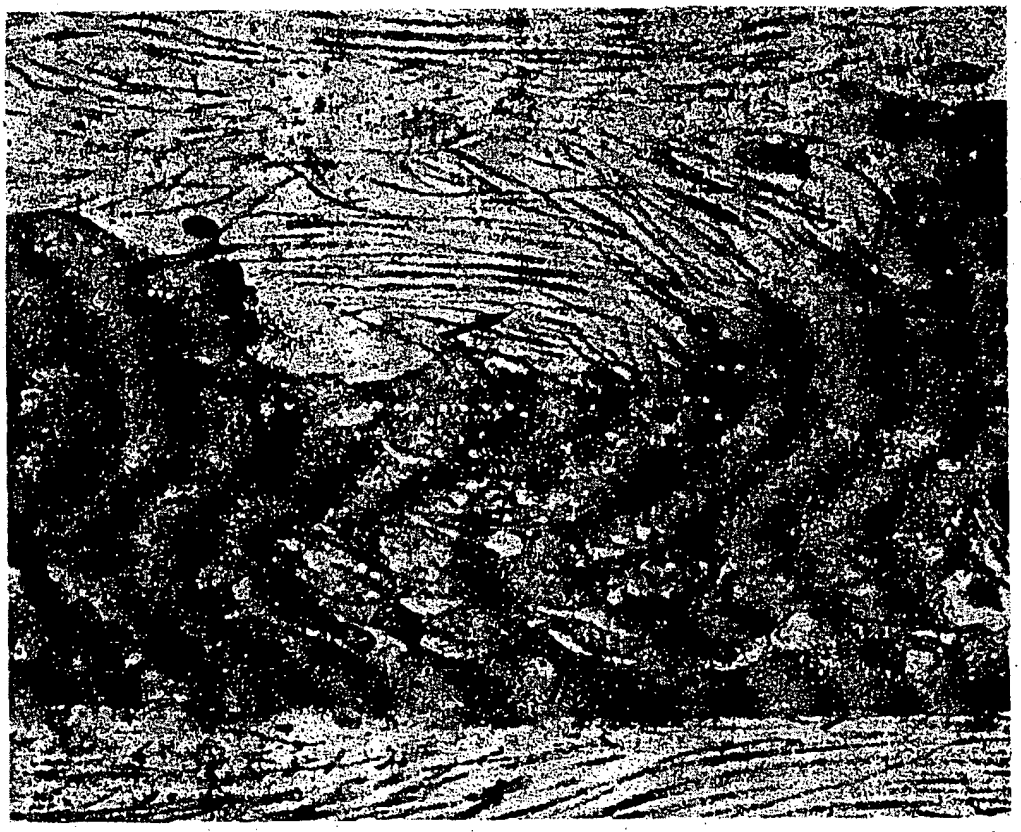

Figure 19. Transmission electron micrograph of Achilles tendinosis revealing active protein *(small arrow)* and collagen fibril production *(large arrow)* (osmium, original magnification × 48,750).

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Figure 20. Transmission electron micrograph of Achilles tendinosis. Note the prominent lipid storage (L), enlarged lysosomal cavities (LY), and swollen disrupted mitochrondria (M) consistent with severe cell stress response and impending cell necrosis (osmium, original magnification × 10,750).

structure of the collagen matrix that is found quite far from the clinical lesion (Fig. 22). Because all of the tendon is exposed to the same mode or use pattern mechanically, the implication is that stress adaptations may be occurring throughout the entire course of the tendon structure. The patient becomes symptomatic only at a site where focal overload, hypovascularity, or some other influence further reduces cell-stress response capability. When breakdown exceeds repair, the tendinosis cycle is initiated. It should be noted that this patient had a normal serum lipid profile and no evidence of xanthomatosis.

The pathologic changes in this case were reflected in the appearance of the magnetic resonance scan, but they were remarkably inapparent on gross examination of the tendon at surgery (Figs. 23 to 25).

Acute Versus Chronic Clinical Injury Profile

In addition to the histopathologic pattern of cell response to injury, acute and chronic injuries are distinguished by their clinical injury

Figure 21. Transmission electron micrograph of Achilles tendinosis with cholesterol clefts (C), severe mitochondral damage (M), myelin forms (MY), and cell necrosis (osmium tetroxide, original magnification × 13,750).

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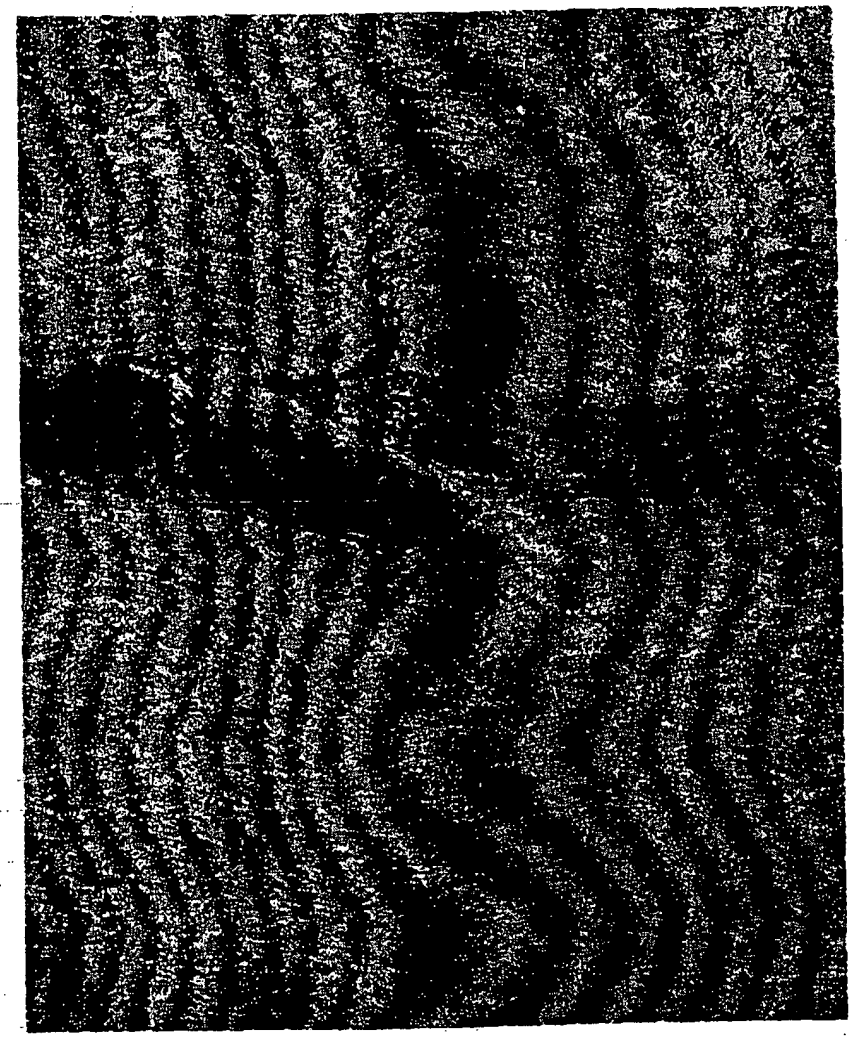

Figure 22. Transmission electron micrograph of Achilles tendon controlled biopsy site 5 cm proximal to tendinosis lesion. Note variability (V) of collagen fibers despite fairly normal crimp (C) pattern. Prominent endoplasmic reticulum (ER) with evidence of protein production implying significant change can coexist throughout the tendon not only at the tendinosis nodule site (osmium tetroxide, original magnification × 8,250).

Figure 23. Preoperative MR scan of Achilles tendinosis. Note the intratendinous signal.

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Figure 24. Gross appearance of Achilles tendinosis lesion. Note fusiform tendon swelling and hyperemic tenovaglum coincidental to intact plantars tendon.

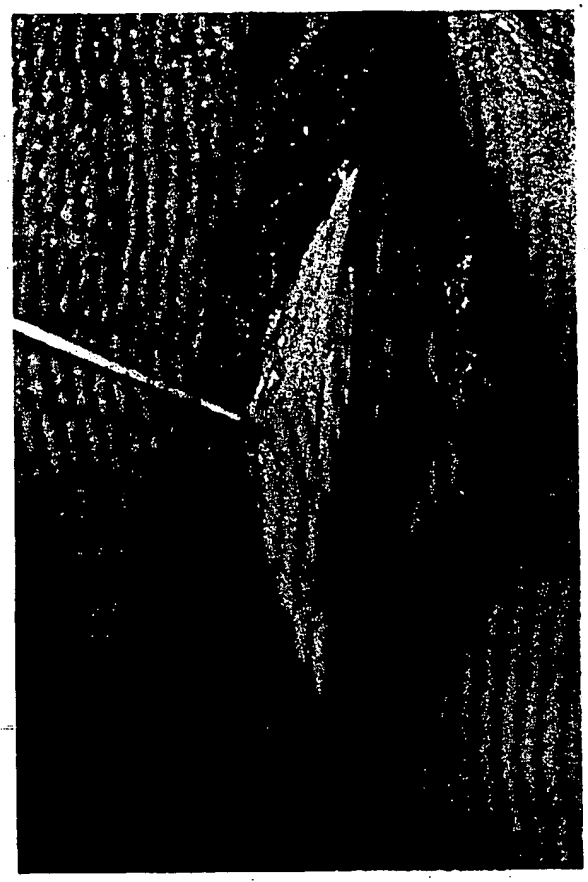

Figure 25. Achilles tendinosis with intraoperative view of longitudinal internal tenotomy. Note the benign gross appearance.

profiles. The acute injury profile is characterized by a defined time of onset with the trauma episode generally observed as a sudden catastrophic occurrence, such as a collision or contact injury, or in the case of a tendon, a spontaneous midsubstance disruption (Fig. 26). At the moment of injury, pain is likely to be severe. This is typically followed by a period of gradually decreasing pain as inflammation is treated intensively. Pain eventually falls below an arbitrary threshold at which time the patient will feel well. When pain is no longer inhibiting, the athlete will request a return to activity; however, when the biologic curve of wound healing is plotted versus the subjective pain response over time, a potential period of reinjury vulnerability appears. The duration of this period of vulnerability is proportional to the original severity of the structural damage, the rate of healing of the given individual, which is likely to be slower with age, the nature of the target tissue that is injured, and lastly the expected demand or load exposure upon return to sports. The period of vulnerability after an acute injury would in theory be lengthened by any raising of the arbitrary pain threshold of the athlete or by any rapid removal of the subjective pain (for example, with aggressive anti-inflammatory treatment or analgesic treatment). It would be lengthened by the adverse

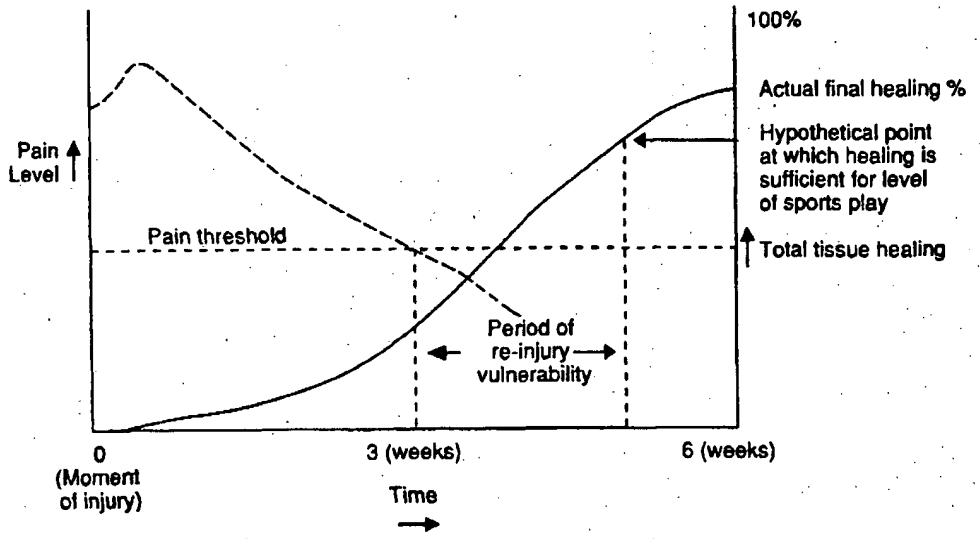

Figure 26. Hypothetical profile of acute macrotraumatic tissue injury. This profile is typical of an acute partial tendon strain or the pattern of healing in other acutely injured connective tissues such as a lateral-collateral ligament sprain in the ankle. Curved dashed line = pain; curved solid line = tissue healing.

effects of any inappropriate immobilization, but it would be shortened by functional rehabilitation or protective bracing that would either expedite fibrogenesis or decrease tensile load on a tendon.[99] Because research has suggested that an injured connective tissue may attain only 70% to 80% of original structural and biomechanical integrity after as much as 12 months,[139] the period of vulnerability in these injuries can be lengthy, implying the need for protected activity despite the absence of pain, and an ongoing rehabilitation program to recruit muscular support.[113]

Chronic soft-tissue injuries differ from acute injuries in several important ways (Fig. 27). The moment of injury, in the athlete's perception, may be a moment of noxious pain. This often occurs after overexertion such as a long-distance run or intense throwing, resulting in pain becoming insidiously inhibiting over a period, or explosively disabling hours or days after the event. Muscle, tendon, and synovial structures typically evidence this type of stress response to sports activity. The examiner's inquiry about the preinjury training patterns and cumulative load exposures is critical to understanding why this type of tissue response has been triggered. For instance, a careful history in a marathon distance runner might reveal that an inadequate amount of time was spent in prerace preparation and that several weeks of mild, but not inhibiting, pain symptoms had been generated by abusive training before the actual moment of injury. This is the transitional injury pattern. In theory, subclinical injury and dysfunction, i.e., microtrauma, precede the moment of conscious injury. The implication is that damage has been accumulating for a long time before the first opportunity for medical treatment. This is distinct from acute injury, in which the onset of injury and initial treatment often closely

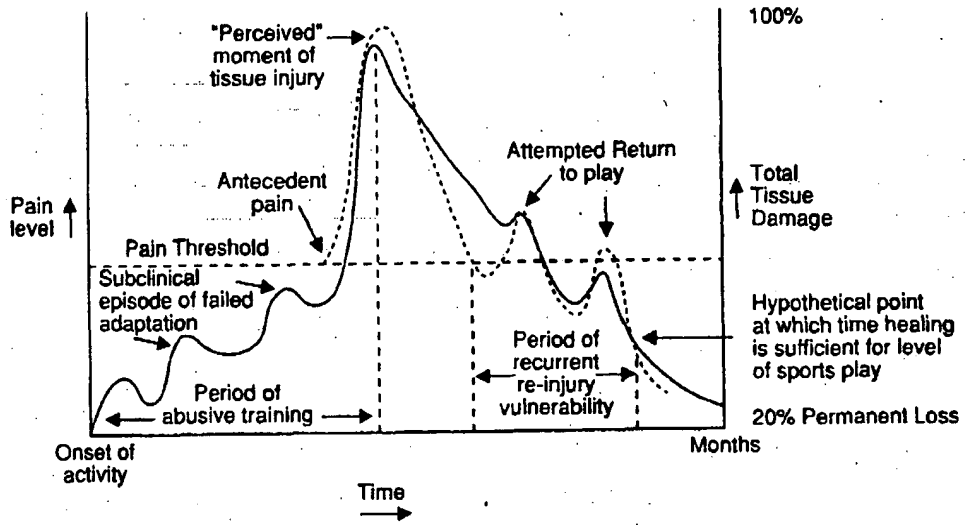

Figure 27. Profile of chronic microtraumatic soft-tissue injury. This profile is typical of overuse tendon injury. Solid line = percentage of tissue damage.

coincide. The accumulation of repetitive scar adhesions, degenerative change, and adverse effects in chronic microtrauma imply that a recovery will be slower. Again, a period of vulnerability to reinjury results, which is increased when conventional anti-inflammatory measures and reduction pain are applied without regard for the lack of adequate structural integrity. In chronic inflammatory injury, it is the history that provides a proper recommendation and adjustment of activity.[82]

The Principle of Transition

As previously defined by Leadbetter,[82, 83] the *principle of transition* states that sports injury is most likely to occur when the athlete experiences any change in mode or use of the involved part (Fig. 28). Transitional injury is rate dependent. Sudden ill-timed activity changes, whether in training or during injury recovery, result in an undesired breakdown response and may outstrip tissue morphostatic efforts by imposing overload or overuse demands on the cell matrix environment. There is growing evidence for a cellular disuse transitional response,[5, 42, 43, 52, 74, 102, 140] as well as an overuse breakdown response.[16, 30, 49, 54, 62, 84, 107, 141] Colosimo and Bassett[31] noted that the only factors correlating with the incidence of jumper's knee were hard playing surfaces and an increased frequency of training sessions. Jozsa and associates[68] have noted that the relationship of complete rupture of the Achilles tendon to a sedentary lifestyle; although the issue is not specifically addressed in their article, it is likely that many of these injuries occurred in the transition from inactivity to activity. Clement et al,[30] in a study on Achilles tendinitis and peritendinitis, were able to identify a training

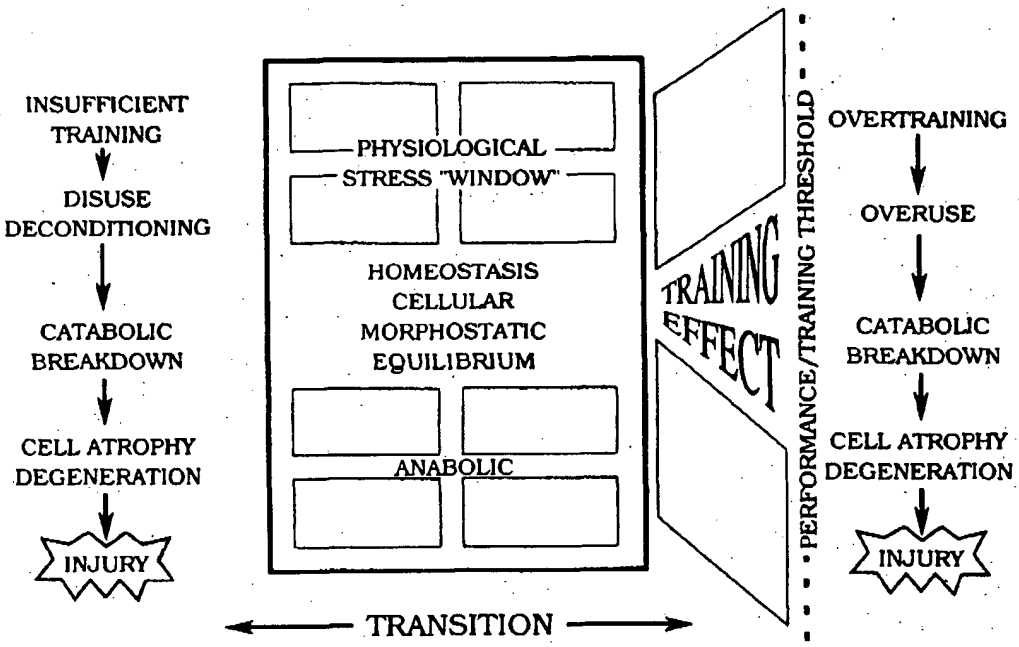

Figure 28. Principle of transition: the more rapid the transition, the greater the risk. (*From* Leadbetter WB: The physiology of tissue repair. *In* Athletic Training and Sports Medicine, ed 2. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1991, p 96; with permission.)

error as the primary etiologic factor in more than 75% of all cases. Of these, the majority represented a sudden increase in mileage. Too rapid a return to activity was also noted as a prime cause of reinjury. Ilizarov,[58] in an attempt to determine the influence of rate and frequency of osseous distraction on cellular behavior, was able to identify a window of tolerable distraction rate of 1 mm per day with as many as 60 incremental lengthenings, thereby creating a gradual transition stress response. He found the rate effects proportional to the growth of the fascial fibroblast and capillary ingrowth.[58] Examples of transitional risks include any attempt to increase performance level, improper training, changes in equipment, environmental changes such as new surface or different training altitudes, alterations in frequency, in intensity, and in duration of training, attempts to master new techniques, return to sport too soon after injury, and even body growth itself. Transition theory correlates with current recommendations on periodization in athletic training.[137]

Wolf's Law of Soft Tissue

Tendon structures are subject not only to tensile load but also to high compressive forces. Such compression occurs extrinsically at sites of pulleys and bony prominences[4]; intrinsic compression is the result of a cyclic torque load seen secondary to pronation of the foot in the Achilles tendon, in the anterior cruciate ligament during the rotatory movement of the knee, and in the rotator cuff during torque about the

shoulder. Vogel[132] has demonstrated an accumulation of large molecular weight proteoglycans in regions of human posterior tibial tendon posterior to the medial malleolus, concluding that there was a synthetic stress response as a physiologic adaptation to compressive forces. Similar findings were noted in the anterior cruciate ligament tissue,[132] as well as in the bovine flexor tendons, where fibrocartilaginous matrix metaplasia is a common finding.[75] Woo,[139] in analyzing the mechanical properties of tendon and ligaments, have theorized an ideal homeostatic level of stress and strain duration to maintain mechanical properties and tendon mass. Frank,[42] in a review of cellular load response to tendon loading, theorized the existence of a possible degradative pathway blockade by an inhibitor to explain observed proteoglycan accumulations under stress. Quoting Gillard, he noted that the apparent cell-mediated changes in glycosaminoglycan content of different areas of a tendon can be demonstrated in response to both relief and return of compression in tensile loading. Later work verified that this was in proportion to the qualities of the changing load conditions. This has led to further observations that cells, collagen, and matrix in tensile and pressure zones of different tendons are in fact different. Whether these effects are mediated by cytoskeletal deformation or are due to as-yet-unproven local piezoelectric effects of matrix on cells is unknown. It is interesting to note the secondary increases in phospholipase A2 arachidonic acid and prostoglandin E synthesis in loaded bone cells, however, is not known at this mechanism exists in tendon.[36, 42, 43] Elliott,[37] in an extensive review, notes the importance of transmitted tension as a stimulus to the transected tendon; tendon fails to heal if the tendon muscle was excised. Based on these and similar observations, Amadio[4] has provided a proposed scheme for Wolf's law of soft tissue (Fig. 29).

Epigenic and Genetic Influences on Tendon Cell Matrix Response

There are both epigenetic and genetic influences on tendon cell matric response. *Epigenic factors* are defined as those factors that can influence the phenotypic expression (i.e., protein production) of the cell without altering the genone.

Vascularity, hormonal influence, and rest may exert an epigenetic influence on tissue injury healing. Aging may be considered to have both an epigenetic and genetic role in injury response.

Aging is best characterized by a failure to maintain homeostasis under conditions of physiologic stress. The salient characteristic of aging is not so much a decrease in basal functional capacity as it is in a reduced ability to adapt to environmental stress.[114, 115]

Menard and Stanish[95] note that the tendon collagen fiber possesses all of the cross linkages it will ever have shortly after its synthesis.[11] During maturation, reducible cross linkages gradually stabilize.[38] This results in a less compliant collagen fiber subject to shear stress injury. Aging also is accompanied by significant decrease in tendon glycosaminoglycan concentration. There are extensive data on the aging of

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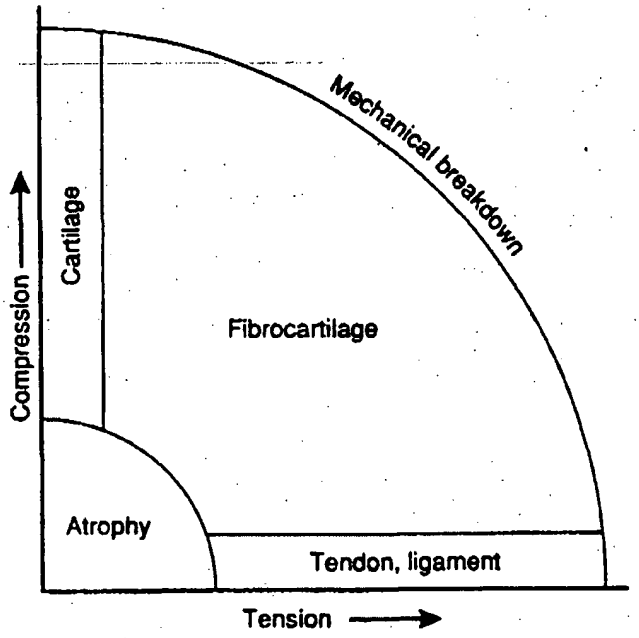

Figure 29. Theoretical schema for Wolff's law of soft tissue. (*From* Amadio PC: Tendon and ligament. *In* Cohen IK, Diegelmann RF, Lindblad WJ (eds): Wound Healing: Biochemical and Clinical Aspects. Philadelphia, WB Saunders, 1992, p 388.)

cells in vitro.[50, 53, 88, 96, 98, 112] Collagen synthesis has long been thought to decrease with age; however, this decrease may be overcome in the presence of ascorbic acid. Generally, aging results in changes in the matrix integrity and in the rate of wound healing, although aging does not prevent adequate *clinical* wound healing, which can be stimulated by physical training. Ippolito[59, 60] has documented morphologic, immunologic, and biochemical aging changes. With aging, collagen fibers increase in diameter, vary more in thickness, and there may be an overall increase in insoluble collagen.[59, 60] These morphologic changes correspond to biochemical changes that include a decrease in proteoglycans and a decrease in water content. Parallel changes in elastic fibers also occur. With age, adaptation requires a longer interval of rest and recovery. This is presumably related to the documented down regulation in the cellular biology of the older athlete. With injury, however, the biochemical and morphologic character of tendon tissue may change. In comparing an area of tendon degeneration in a 25-year-old adult with spontaneous Achilles tendon rupture with that of a normal 24-year-old, Ippolito[59, 60] noted that in the area of tendinosis there was a 34% loss of collagen and an increase in proteoglycans of more than 100% with a significant increase in water and glycoprotein content.

Vascularity has long been thought to play a prominent role in tendon degeneration,[35, 79, 121, 129] especially in the supraspinatus portion of the rotator cuff, in the Achilles tendon, and at sites of extrinsic bone pressure. Since the injection study of Rathbun and McNab,[109] a watershed area in the distal supraspinatus tendon had been offered for an explanation of the etiology of rotator cuff degeneration. Chanski and Ionnotti,[23] in an extensive review, conclude that the vascularity in

the critical zone of the supraspinatus tendon is actually hypervascular secondary to a low-grade inflammatory incitation with neovascularization after mechanical irritation.[23] Brooks et al[17] likewise came to the conclusion that no significant difference existed between the vascularity of the supraspinatus portion of the rotator cuff, and that factors other than vascularity were important in the pathogenesis of supraspinatus tendon rupture. These assertions tend to shed a different light on the theory of hypoxic intratendinous degeneration and the etiology of tendinosis. Focal load influences on cell matrix metabolism may play as great a role as any proposed diminished vascularity. Wilson and Goodship[138] have measured a core temperature increase of 5°C to 9°C secondary to hysteresis energy losses in the equine superficial digital flexor tendon during exercise. This radiant energy equals 10% of the lost elastic energy upon unloading and is theorized to be potentially cytotoxic. Further research is needed to resolve this question.[18] Whereas there seems to be a preponderance of support for a diminished microvascular debt in the central core of the round tendon and in the distal third of the Achilles tendon,[119] controversy has arisen as to the role of hypovascularity in rotator cuff and supraspinatus tendon degeneration[129] (Figs. 30 and 31).

Hormonal influence on tendon biology primarily relates to estrogen and to insulin. It has been suggested that diminished estrogen levels, premature menopause, or premenopausal hysterectomy may be associated with the incidence of tendinosis in women; no other data are

Figure 30. Intra-operative view of Achilles tendinosis linear internal tenotomy. Note that perfusion from the internal tendon vasculature is hypovascular relative to the epitenon.

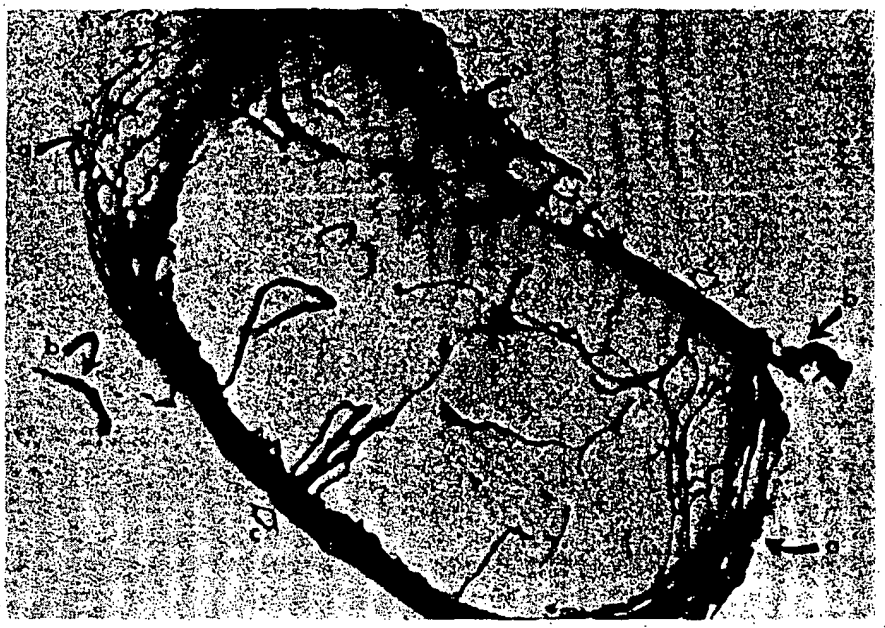

Figure 31. Cross-sectional injection of histologic study of an Achilles tendon vasculature. Note the peripheral distribution with less internal perfusion. (*From* Schatzker J: Intravital observation on the microvascular anatomy and microcirculation of the tendon. Acta Orthop Scand 126(suppl):1–23, 1969; with permission.)

available to support this contention.[100] In addition, diabetics are known to heal with some difficulty.[89]

Rest has long been clinically recognized to aid the patient with a tendon injury. The beneficial role of rest in the therapeutic intervention of the inflammation repair process is experimental and undefined. Although it may be said that rest does not heal; theoretically, cell reparative efforts may catch up in the face of rest. The effects of rest are probably multifactorial and may include improved vascularity in the tendon at rest or represent an improved morphostatic balance between matrix degradation and production. Different forms of rest include total abstinence, protected activity, or altered activity. Such classifications imply a modulation in cell matrix load signal and load recovery phase. There is evidence that repetitive motion and variation of frequency (i.e., cycles) may create a positive reparative signal post-injury.[46] Absolute rest or abstinence does not de facto increase the athlete's potential to tolerate renewed load during participation. Modified load rehabilitative prescription has been shown to be important to any successful return to sports performance.[30, 33, 113, 126]

Genetic influences are implicated in the modulation of tendon cell matrix response based primarily on clinical observations. Nirschl[100] has called attention to the mesenchymal syndrome as a potential cause of failed healing. Tendinosis appears in multiple sites in approximately 15% of patients and in sites not necessarily subjected to obvious overuse. An association among lateral epichondral extensor carpi radialis brevis tendinosis, rotator cuff degeneration, carpal tunnel syndrome, cervical and lumbar disk degeneration, plantar fasciosis, de Quervain's syndrome, and trigger-finger tendinosis has been postu-

lated. Jozsa et al[67] have found blood type O to be statistically related to tendon rupture. It is interesting, as noted by Singer and Jones,[120] that Achilles tendon rupture in children is uncommon and has been encountered only in children whose parents had experienced tendon rupture. Young adult herniated disk syndrome is often seen in the presence of a familial history (author's personal observation). An underlying collagen diathesis has been theorized. In the author's experience, the significance of the mesenchymal theory is in recognizing the patient who presents with frequent tendon complaints disproportionate to the level of activity. In addition to ruling out systemic disease, these patients are unusually vulnerable and must be counseled as to proper participation and moderation in their activity.

The factors leading to potential failed healing response are both intrinsic and extrinsic and are summarized in Table 3.

Sources of Pain in Tendon Injury

The sources of tendon pain are multifactorial and include both paratenon as well as intrinsic cellular and biomechanical deformation sources. The synovial site is capable of secreting a wide array of inflammatory mediators, in particular interleukin-1 and prostaglandin E_2. How movement and friction activate these cells is not known,[41, 44, 61, 77, 111] but particles of cartilage and the degradation of other protein molecules may incite a synovial reaction.[111] The intrinsic tendon fibroblast is capable of producing inflammatory mediator proteins under repetitive stress.[3] Elongation underload of the tendon beyond its elastic limit may trigger nociceptors as well as myotendinous reflexes.[24, 33] There would appear to be a distinction between the pain due to inflammation and that due to degeneration (author's unpublished

Table 3. FACTORS LEADING TO FAILED TENDON HEALING

Intrinsic
Vascular vulnerability
Limited cell function potential
Limited cellularity
Aging
Genetic predisposition (mesenchymal syndrome, collagen crosslinking, etc.)
Irreversible change, cystic calcific degeneration
Hormonal
Other (autoimmunity, etc.)
Extrinsic
Overt
Continued self-abuse
Improper training (overstimulus or inadequate stimulus)
Improper technique
Improper equipment
Harsh environment
Covert
Joint instability
Extrinsic pressure
Biomechanical fault

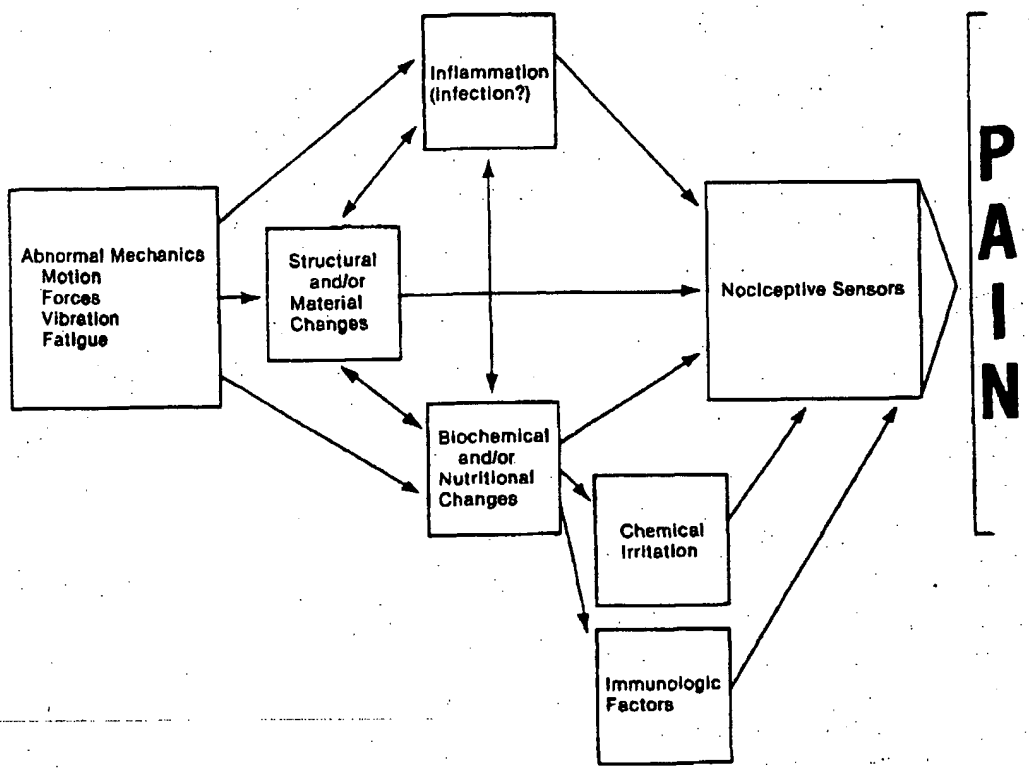

Figure 32. Possible mechanisms of musculoskeletal pain. (*From* White AA III: The 1980 symposium and beyond. *In* Frymoyer JW, Gordon SW (eds): New Perspectives in Low Back Pain. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1989, pp 3–17; with permission.)

observation). The pain of inflammation evolves from excessive loading with cell matrix and distal damage producing the onset of the inflammatory cascade typical of macrotraumatic or synovial irritation.[133] Degenerative pain evolves from excessive cyclic loading, which results in matrix molecular damage, loss of tissue strength, resultant increased deformation with loading, and stimulation of mechanoceptors.

A scheme for musculoskeletal pain that is applicable to tendon injury has been provided (Fig. 32).

Further Clinical Implications

A statement that tendon healing progresses in a typical pattern regardless of the mechanism of injury[24] is untenable in light of the previous discussion. The statement that the body's immediate and long-term responses to physical trauma are essentially the same for all types of athletic injuries,[15] or that a tissue's response to injury, no matter what the cause or type of injury, is inflammatory,[54] must be qualified. The type of injury has a great deal of influence over the wound healing process.[63] The size of the wound, the extent of the initial tissue damage, the presence or absence of any coincident contam- synovial structure versus extra-articular tendon, may dictate the rate of

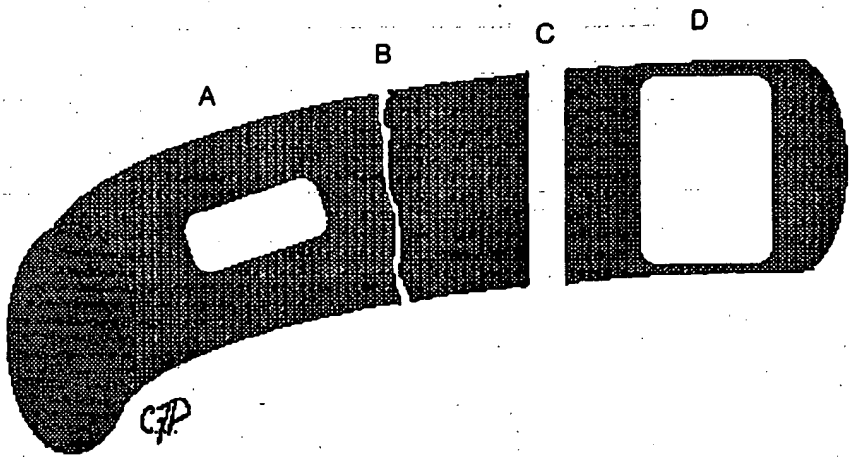

Figure 33. Hypothetical model of tendon lesions. *A*, Intratendinous shear lesion. *B*, Pinhole tear. *C*, Gap. *D*, Intratendinous cystic degeneration (tendinosis). Different mechanisms of healing repair response are implied.

recovery and its adequacy (Fig. 33). The initial events in the resolution of microtraumatic wounds, in particular the metabolic activity and pattern of protein synthesis of the mesenchymal cell population found in tendinosis lesions, is not well understood.

The tenocyte has been theorized to have limited capability for mitosis or increased collagen production beyond maintenance and has been called an end-stage cell.[28] Aging tenocytes show a marked decrease

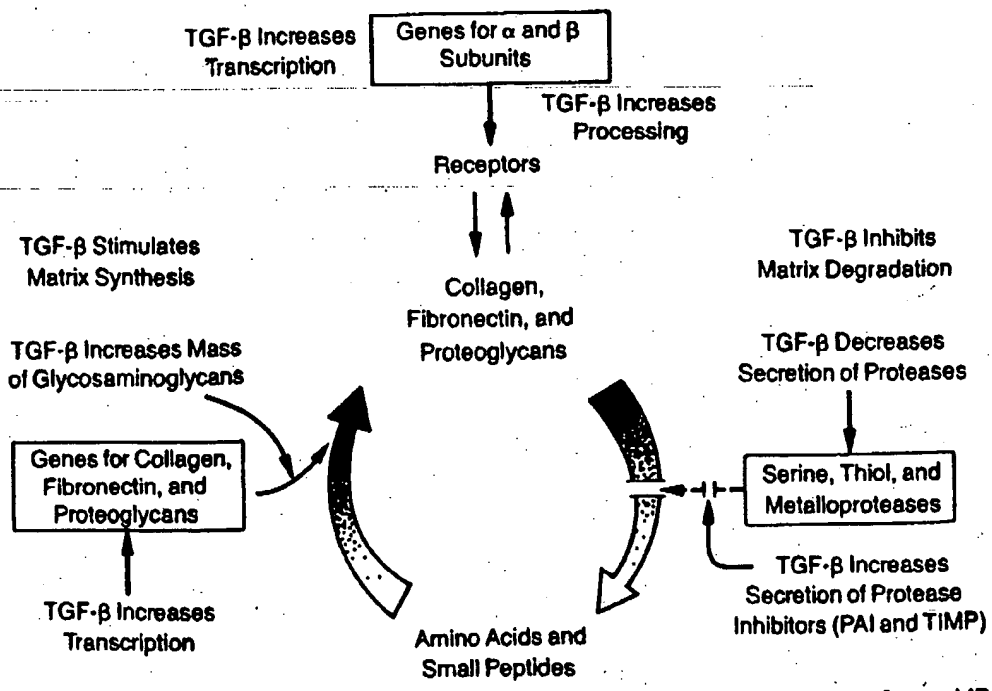

Figure 34. The role of TGF-β in the stimulation of extracellular matrix. (*From* Sporn MB, Roberts AB: Transforming growth factor-β: Multiple actions and potential clinical applications. JAMA 262:938–941, 1989; with permission of the American Medical Association, Inc.)

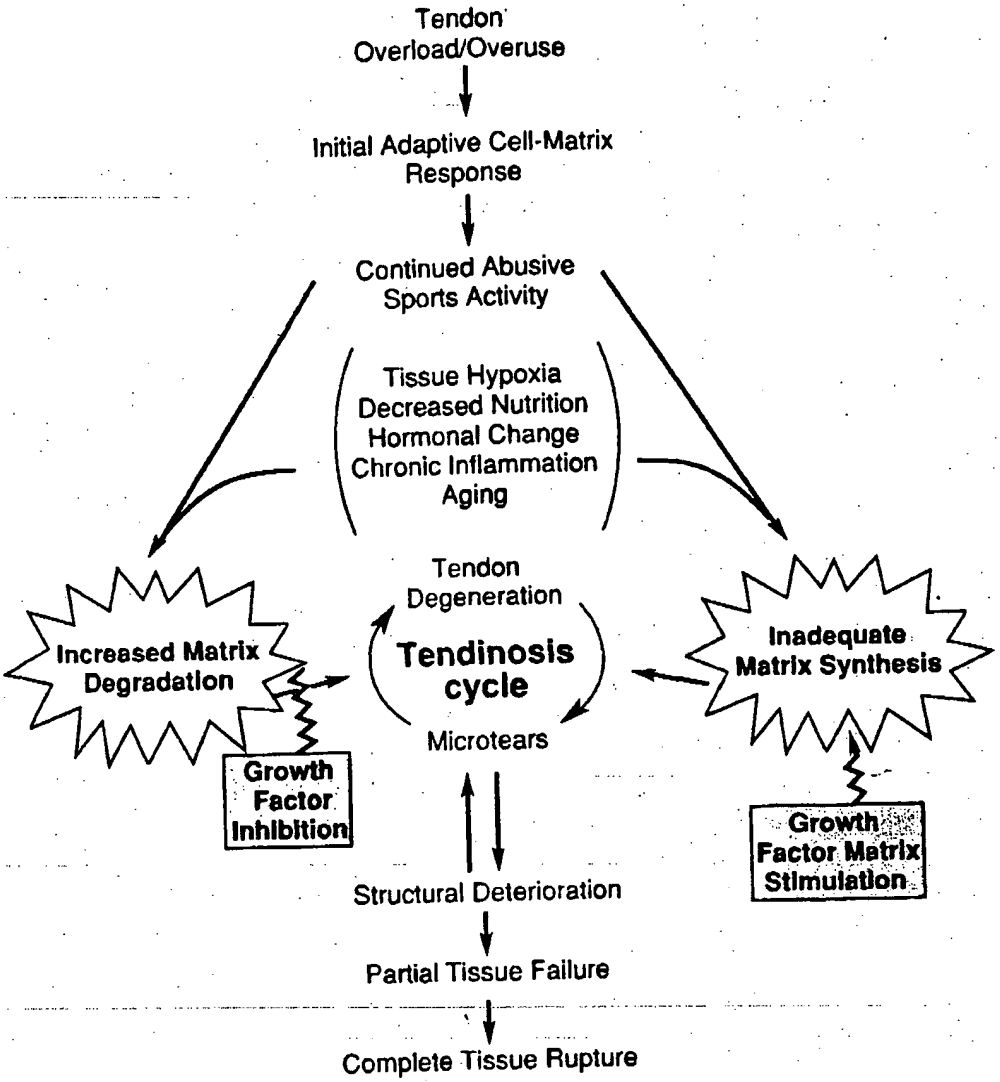

Figure 35. Theoretical application of growth factor therapy in tendon injury.

in intracytoplasmic organellae responsible for protein synthesis. Senescence in the tenocyte parallels the known aging phenomenon occurring in fibroblasts throughout the body.[20] Other histopathologic studies, however, including our own,[85] have suggested that significant reparative response capability resides within the activated tenocyte postinjury or after overload/overuse stimulation. The findings of hypercellularity, increased organelle activity, and patterns of scar deposition intermingled with scattered cell necrosis, degeneration, and collagen disorganization suggest a different theory, namely that it is the imbalance of tenocyte reparative efforts and a failed adaptation as opposed to an inherent lack of healing capability that limits the outcome in cumulative traumatic injury. If such capability still resides within the genome, then therapeutic efforts can target its potentiation.

As with other connective tissues, the metabolism of tendon tissue is not regulated by a dominant central control mechanism.[21] Rather,

tendon cells seem to function in an interdependent way with their matrix. To what degree mutual local control over neighboring cells exists is a matter for ongoing investigation. Normally, a homeostatic balance is maintained between matrix synthesis and degradation; in stressed states, an adaptive response is elicited. Cytokines (which may be defined as soluble products, mostly protein peptides, released from one cell that can modulate the activity of other cells [paracrine] or the same cell [autocrine]) play a critical role in the process of cell communication. Individual cytokines may have multiple biologic activities, and several cytokines may share common functional properties. Cytokines are best understood as analogous to letters in an alphabet, with cellular messages changing according to sequences and the interaction between several cytokines simultaneously. In the open system of connective tissue metabolism, clinical attempts to modulate wound healing have been challenging. The same peptide may affect a cell entirely differently in vitro versus in vivo. Based upon these observations and the observations of Sporn and Roberts and others,[97, 110, 124] a theoretic model can be proposed for the pathogenesis of sports-induced tendinosis as well as the potential therapeutic role or growth factors, notably transforming growth factor beta (Figs. 34 and 35).

CONCLUSION

The major mysteries of injury and repair have always been and continue to be *what* in the injury stimulates repair, and *how* does the wound recognize that it is no longer needed—that is, *why* does healing stop?[56] Once thought to be inert biologically, tendons are best appreciated as a heterogeneic group of structures with variations in cell character, collagen orientation, collagen cross linking, vascularity, configuration, load pattern, biomechanical profile, shape, and the presence or absence of a synovial lining. Tendons have the *potential* to manifest one or several stress adaptation behaviors depending upon the mechanism of injury and the nature of the continuing sports demand. Transition plays an important role in the determination of this process.

Since Vichow's work,[131] modern pathology has defined injury in cellular terms. The study of tendon injury is the study of cell injury and its matrix milieu as an expression of pre-existing capacity to adapt to such injury on the part of the injured or intact cell.[114] Today, sports injury is further defined by the degree to which normal mechanical properties in function are lost as a consequence of both cell and matrix injury. The modulation of these cell matrix responses regardless of the method provides an intriguing challenge.

ACKNOWLEDGMENT

The author would like to thank Ingrid Major, Janelle Owen, and K. Blanch Emore for their excellent secretarial assistance.

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CLINICS IN SPORTS MEDICINE

Tendinitis I: Basic Concepts

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VOLUME 11 • NUMBER 3 • JULY 1992

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Table of Contents (click to jump to sections)

What is Carpal Tunnel Syndrome?
Carpal tunnel syndrome occurs when tendons or ligaments in the wrist become enlarged, often from inflammation, after being aggravated. The narrowed tunnel of bones and ligaments in the wrist pinches the nerves that reach the fingers and the muscles at the base of the thumb. The first symptoms usually appear at night. Symptoms range from a burning, tingling numbness in the fingers, especially the thumb and the index and middle fingers, to difficulty gripping or making a fist, to dropping things. Some cases of carpal tunnel syndrome are due to work-related cumulative trauma of the wrist. Diseases or conditions that predispose to the development of carpal tunnel syndrome include pregnancy, diabetes, and obesity.

Is there any treatment?
Carpal tunnel syndrome is treated by immobilizing the wrist in a splint to minimize or prevent pressure on the nerves. If that fails, patients are sometimes given anti-inflammatory drugs or injections of cortisone in the wrist to reduce the swelling. There is also a surgical procedure in which doctors can open the wrist and cut the ligament at the bottom of the wrist to relieve the pressure. However, only a small percentage of patients require surgery.

What is the prognosis?
Approximately 1 percent of individuals with carpal tunnel syndrome develop permanent injury. The majority recover completely and can avoid reinjury by changing the way they do repetitive movements, the frequency with which they do the movements, and the amount of time they rest between periods when they perform the movements.

What research is being done?
Much of the on-going research on carpal tunnel syndrome is aimed at prevention and rehabilitation. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) funds research on carpal tunnel syndrome.

Select this link to view a list of studies currently seeking patients.

Organizations

American Academy of Orthopaedic Surgeons/ American Association of Orthopaedic Surgeons
6300 North River Road
Rosemont, IL 60018
hackett@aaos.org
http://www.aaos.org
Tel: 847-823-7186
Fax: 847-823-8125

American Chronic Pain Association (ACPA)
P.O. Box 850
Rocklin, CA 95677-0850
ACPA@pacbell.net
http://www.theacpa.org
Tel: 916-632-0922 800-533-3231
Fax: 916-632-3208

National Chronic Pain Outreach Association (NCPOA)
P.O. Box 274
Millboro, VA 24460
ncpoa@cfw.com
http://www.chronicpain.org
Tel: 540-862-9437
Fax: 540-862-9485

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
National Institutes of Health, DHHS
31 Center Dr., Rm. 4C02 MSC 2350
Bethesda, MD 20892-2350
NIAMSinfo@mail.nih.gov
http://www.niams.nih.gov
Tel: 301-496-8190 877-22-NIAMS (226-4267)

Centers for Disease Control and Prevention (CDCP)
U.S. Department of Health and Human Services
1600 Clifton Road, N.E.
Atlanta, GA 30333
inquiry@cdc.gov
http://www.cdc.gov
Tel: 800-311-3435 404-639-3311/404-639-3543

Occupational Safety & Health Administration
U.S. Department of Labor
200 Constitution Avenue, NW
Washington, DC 20210
http://www.osha.gov
Tel: 800-321-OSHA (-6742)

Related NINDS Publications and Information

- Carpal Tunnel Syndrome Fact Sheet
  Carpal Tunnel Syndrome fact sheet compiled by the National Institute of Neurological Disorders and Stroke (NINDS).

Publicaciones en Español

- Síndrome del Túnel Carpiano
  Información del Síndrome del Túnel Carpiano/Spanish-language fact sheet on carpal tunnel syndrome compiled by the National Institute of Neurological Disorders and Stroke (NINDS).

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Return to top

Last updated December 03, 2004